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Clinical Viability Study of Preattentive Visual Search Glaucoma

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CLINICAL VIABILITY STUDY OF PREATTENTIVE VISUAL SEARCH IN GLAUCOMA

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ABSTRACT

***Background/Aim*:** Previous research has shown that several clinical conditions cause increased pre-attentive visual search (PAVS) times, implying reduced parallel search capabilities in glaucoma, DLB dementia AND Parkinson's disease. The purpose of the research reported here was two-fold:

- To examine for the first time the effect of a number of variables on PAVS performance including optical blur, age, retinal eccentricity and perceptual learning. Such investigations are designed to elucidate the nature of best clinical practise and to determine whether the test remains viable in the presence of such potentially confounding variables.

- To analyse the efficiency of PAVS in cases of established glaucoma; glaucoma suspects and age-matched normals. Such an investigation is designed to determine the differential diagnostic capacity of the current test and to provide diagnostic cut-off performance indices to facilitate clinical categorisation of patients.

Methods: Suitably configured flicker, motion displacement and orientation pop-out stimuli were presented to subjects on a computer monitor. The subjects' task was to accurately locate the pop-out target from among 120 distractors on either left or right of the monitor as rapidly as possible. PAVS performance was determined through analysis of the speed of accurate target location and its relation to the individuals' complex (non-preattentive) reaction time.

Results: The current test remains largely resistant to the sensory degradation effects of optical blur and retinal eccentricity. Only the orientation task requires a reasonable level of visual acuity (better than 6/18). The perceptual learning effect is minimal, therefore little practice is required prior to clinical application of the test. The sensory and motor

effects of age are rendered negligible through development of a measure of perceptual search ability. The test therefore remains clinically robust. In relation to glaucomatous neuropathy, the test yields consistently high sensitivity and specificity for each task and thus appears to provide a suitable means of glaucoma detection.

Conclusions: All investigations thus far indicate that, at the very least, the test provides a simple, rapid and accurate means of screening for the effects of glaucomatous optic neuropathy. Its capacity to differentiate glaucoma from suspects suggests its diagnostic ability extends beyond that achieved by conventional perimetry. Longitudinal analysis should confirm whether this is true.

DECLARATION

I certify that this thesis which I now submit for examination for the award of PhD, is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

This thesis was prepared according to the regulations for postgraduate study by research of the Dublin Institute of Technology and has not been submitted in whole or in part for an award in any other Institute or University.

The work reported on in this thesis conforms to the principles and requirements of the Institute's guidelines for ethics in research.

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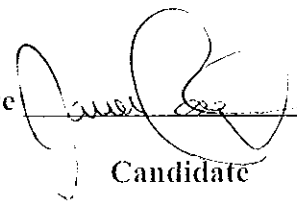
Signature  Date 13/12/06

Candidate

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List of Abbreviations

American Academy of Ophthalmology (AAO)

Dementia with Lewy Bodies (DLB)

Choice Reaction Time (CRT)

Dorsal Lateral Geniculate Nucleus (LGNd)

Intraocular Pressure (IOP)

Low Tension Glaucoma (LTG)

Magnetic Resonance Imaging (MRI)

Ocular Hypertension (OHT)

Optical Coherence Tomography (OCT)

Optic Nerve Head (ONH)

Perceptual Search Ability (PSA)

Primary Open Angle Glaucoma (POAG)

Posterior Ciliary Artery (PCA)

Preattentive Visual Search (PAVS)

Pseudoexfoliative Glaucoma (PXG)

Retinal Nerve Fibre Layer (RNFL)

Short Wavelength Automated Perimetry (SWAP)

Simple Reaction Time (SRT)

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INTRODUCTION & BACKGROUND THEORY

CHAPTER 1

INTRODUCTION

1.1 Project Background

The cranial nerves have evolved to permit the human organism to sense and respond to the immediate environment. That more cranial nerves serve the eye than any other single structure in the body gives an indication as to the importance of vision in human evolution. The question as to whether and when people can perform perceptual or mental operations in parallel began to receive experimental treatment in the late nineteenth century (for review see Townsend, 1990). It was a natural question for the emerging discipline of psychology because it is inherently related to the capacity of the mind and how that capacity is allocated to cognitive and perceptual endeavours. Such endeavours necessarily require conscious attention to be deployed to the task at hand. Early scientists must have recognised the importance of vision and visual processes in attentional deployment. Any capacity limitations on early vision would have consequences for cognition.

Thus, the role of vision in attention has become a cornerstone in research exploring the workings of the mind. One of the major tools for investigating primitives of the visual system and the role of attention in visual object recognition has been the visual search task, in which an observer searches for a pre-specified target among an array of distractor non-targets. A key finding to emerge from this paradigm is that search time and accuracy vary systematically with the type of target and the number of distractors. Neisser (1967) was the first to introduce the concept of a dichotomous search system involving attentive (serial) and preattentive (parallel) processes, which are with and without capacity limitations respectively.

Preattentive visual search (PAVS) allows the visual system to perform a simple analysis of image content simultaneously across an entire image, spanning a wide retinal area. A stimulus within the image that differs in some elementary feature from the background is detected preattentively, and appears to "pop-out" of the pattern (Saarinen, 1996). The role of a preattentive mechanism is at a minimum two-fold. First, it allows for rapid detection of, and attentional deployment to visually important features within the visual field. From a Darwinian perspective, such capability provides obvious evolutionary benefits to survival and development of the species. Second, it permits efficient visual search for consciously defined targets within an often-cluttered environment. Preattentive mechanisms essentially guide attention to the most likely target locations so that the serial "spotlight" does not have to process every possible location. Efficient visual search, comprising overlapping parallel and serial mechanisms, therefore plays a significant role in our daily lives, simplifying common tasks, protecting against potential threats and facilitating our capacity to partake and excel in specialised tasks such as sports, driving and other modern activities. The intricacies of parallel and serial search mechanisms are explored in detail in chapter 2.

While experimental strategies have been deployed to explore the capacities and mechanisms of visual search, very little has been done to investigate the potential of numerous fundamental parameters affecting vision to influence the application and interpretation of a test of preattentive visual search in a clinical test environment. Ahissar and Hochstein (1996 & 1997), Hommel et al. (2004), and Carrasco et al. (1995) have explored the effects of perceptual learning, aging and retinal eccentricity on search performance respectively. The work completed by these and others has yet, to our

knowledge, to be applied so that the observed effects can be incorporated into the design and interpretation of results in a clinical population with the aim of detecting eye disease. One goal of the present study is therefore to explore these parameters (also incorporating the effects of optical defocus which is previously untested) beyond that of previous studies.

If vision is the most important of the special senses, then diseases affecting vision will heavily influence the lives of those they affect. Optic nerve disorders are significant by virtue of their capacity to threaten sight and by their relationship to systemic disease. Glaucoma, defined as a multi-factorial optic neuropathy (AAO, 2005), is a complex condition that is often oversimplified because we do not fully understand its pathophysiology. Complex conditions seldom yield simple solutions. Detecting early glaucoma damage and deciding when to initiate treatment in the glaucoma suspect is therefore a topic of much controversy. Established diagnostic techniques have fundamental flaws that merely serve to enhance the difficulty in providing an accurate early diagnosis. Early diagnosis characteristically yields a more positive prognosis for ultimate visual integrity (Tezel et al., 2001). To this effect, researchers have long been employed in the arduous task of developing more sensitive techniques. While numerous strategies have provided exciting results, no anatomical or psychophysical test has proved sufficient to surpass existing techniques to date. The holy grail of a highly sensitive and highly specific test for pre-perimetric glaucoma detection, if one exists, remains elusive. PAVS is one test that has been shown to be sensitive to glaucoma (Flitcroft et al., 1996) but which has not been further explored; indeed their work provided the inspiration for the present thesis. Previous research has shown that several other clinical conditions cause

increased PAVS times such as DLB dementia (Cormack et al., 2004) and Parkinson's disease (Troscianko & Calvert, 1993).

1.2 Project Aims/Objectives

The objectives of the research reported here were as follows:

- To examine for the first time the resistance of PAVS to **optical blur**. Resistance would enhance the applicability of PAVS as a screening method for glaucoma and other clinical conditions affecting performance of a substantial area of the retina. Lack of resistance might result in increased possibility of false positive outcomes, or at least require good corrected visual acuity to perform the test.

- To analyse the effect of **age** on PAVS efficiency. While age is often associated with a maturity of thought, it also coincides with less desirable effects such as changes in pupil size and losses of sensitivity in the retina and along the visual pathway (Johnson et al., 1989). Age-specific changes in visual search performance have been reported for reaction time based search tasks (Madden & Allen, 1995). Given the response time paradigm employed, determination of the expected normal PAVS time for each task across different age groups is an essential step in the PAVS test development. The effect of age (if any) on processing speed and motor response is important given the age profile of potential glaucoma patients.

- To determine the timeframe required to reach a **perceptual learning** plateau for PAVS test performance. This has implications for the clinical viability of the test. Psychophysical tests are known to elicit a learning curve (Wood et al., 1987; Wild

et al., 1989; Ahissar & Hochstein, 1996), and as such generally require a task specific period of practice (relating to task complexity – Ahissar & Hochstein, 1997) prior to test completion.

- To analyse the effects of **eccentricity** on PAVS efficiency. The sensitivity of the peripheral retina varies according to the task/target type. Typically, targets presented near to fixation are identified more easily than more peripheral targets (Carrasco et al., 1995). In a response time rather than threshold paradigm, evaluation of central versus peripheral performance is important. Any effect would need to be addressed in reconfiguration of suitable stimuli for testing of clinical conditions such as glaucoma which affect extra-foveal vision.

- The ultimate project aim is to analyse the suitability of the current test for detection of early **glaucoma**. Glaucoma remains a leading cause of blindness in Ireland (Kelliher et al., 2006) and across the world (Quigley, 1996). Many cases of early glaucoma go undetected, some of which may be due to over reliance on poor screening techniques. To analyse the efficiency of PAVS in cases of established glaucoma, glaucoma suspects and age-matched normals is a crucial first step to determine the applicability of the current test configuration to early diagnosis. It may also serve to elucidate necessary design modifications to PAVS test parameters.

1.3 Expected Results

Pre-attentive vision is a global visual function that can perform a simple analysis of image content simultaneously across an entire image. Consequently it is a reasonable assumption that PAVS is dependent on neural mechanisms being intact across the retina, not just at the fovea. If this is the case, a suitably configured PAVS test might be able to detect any retinal disease or other condition that produces damage across a significant area of the visual field. If pop-out does not occur, for example because glaucoma is present, search will be more serial in nature and response times will increase accordingly.

The current test employs three target types (see section 6.2), differing significantly from the background distractors in terms of flicker, vertical displacement, and orientation, so that each should pop-out if preattentive mechanisms are functioning. As such the battery of tests might be expected to differentiate glaucoma from normality on the basis of compromised retinal and/or neural function in the former. Evaluation of PAVS response times among different glaucoma subgroups may also elucidate whether different pathophysiological mechanisms have different effects on preattentive search efficiency in cases of early glaucoma.

Analysis of results in other experimental paradigms should clarify certain functional aspects of test implementation such as the amount of practice required prior to data collection and the necessity of optical correction and/or impact of reduced best-corrected visual acuity on search performance. The suitability of certain aspects of the current test parameters for clinical use will also be determined, and the results used to decide whether

and how best to incorporate any required changes, for example, to account for any observed effects of age, glaucoma or target eccentricity on PAVS performance.

1.4 Research Benefits

The principal benefit of the current research project is a gross determination of the suitability of the present design test of PAVS efficiency for clinical implementation as a screening tool for glaucomatous optic neuropathy. The development and validation of a novel test of retinal and/or neural function that could be employed in routine glaucoma screening in clinical practise is of obvious merit. The current test design can be readily incorporated into clinical or hospital practise using existing computer equipment, it could be made available to download anywhere in the world as a low-cost alternative to other techniques, and because of its short test time and ease of use, it provides a patient and practitioner friendly means of assessing visual function. The current paradigm provides for evaluation of the viability of the test for screening purposes. Longitudinal analysis of glaucoma suspects would be required to determine whether the test correctly identifies those glaucoma patients without perimetric field loss who subsequently develop field loss in the absence of treatment, thereby fully describing the potential role of PAVS mechanisms in glaucoma diagnosis.

The effects of optical blur on PAVS have, to our knowledge, never been previously examined. As such it represents a novel investigation into the capacity of vision to guide attention under a potential cause of duress. The results of this investigation have been peer reviewed and accepted for publication (Davison & Loughman, 2006).

Other investigations serve to assess the practicalities of the test, providing results that can be incorporated into a suggested clinical routine or screening strategy should the test become commercially available.

In summary, the current project serves to more completely assess the design structure of the test, the variables affecting its clinical application and the suitability of the test for routine glaucoma screening. Such steps are essential if the ultimate aim is to develop a test that has clinical validity.

CHAPTER 2

VISUAL SEARCH

2.1 Visual Search – Introduction

The average person is continuously involved in numerous visual search tasks: looking for the car keys, finding a friend in a crowd, or searching for that ever-more elusive car park space. The above constitute examples of mostly conscious, top-down or user-driven search tasks.

The detection of the sudden appearance of a possibly threatening target such as a high-speed car in the immediate vicinity, represents an additional search strategy which is a mostly subconscious, bottom-up or stimulus-driven system mediated by the rapid and accurate detection of a limited subset of visual properties by the visual system.

The combined activity of these search systems facilitates our ability to detect targets that are either consciously defined or instinctively visually important. This ability is not trivial and has become increasingly important in our cluttered visual environment, and humans remain highly efficient at finding visual stimuli in a world filled with other, distracting stimuli.

The visual system cannot fully process all of its input. There is not enough room in the skull for all of the neural hardware that would be required to perform all visual functions at all locations of the visual field at the same time (Tsotsos, 1990). The visual system has two approaches to this problem.

The first is to discard input. Thus, the retinal image is processed in its full detail only at the fovea. In the periphery, information is much more coarsely sampled. Receptors are

spaced more widely, ganglion cells receptive fields are larger, and the cortical representation of the periphery is smaller (Wilson et al., 1990; White et al., 1992).

The second approach is to process information selectively. A large set of visual functions, for example, reading, can be performed only in a restricted part of the visual field at any one time. Other functions operate across the entire visual field simultaneously (including preattentive processing). As Neisser (1967) suggested, there are parallel processes that operate over large portions of the visual field at any one time, and there is a second set of limited-capacity processes that are restricted in their operation to a smaller portion of the visual field; these limited-capacity processes must be deployed serially from location to location.

When we open our eyes on a familiar scene, we form an immediate impression of recognizable objects, organised coherently in a spatial framework. This efficient performance suggests that the neural systems sub-serving vision maintain highly detailed information about the entire visual scene.

Experiments, possibly going all the way back to those conducted by Hamilton in 1859 (Townsend, 1990), have attempted (empirically, if not exactly experimentally in Hamilton's case) to determine how quickly an individual can perform mental or perceptual operations based on vision. One of his techniques was to toss several dice on his desk and try to assess "instantaneously" the number of dots showing.
More careful experimental paradigms now suggest that the visual system maintains detailed information about only a handful of objects at any one time, those that we happen

to be "paying attention to", and that our visual experience of full knowledge of our visual surroundings must, in some sense, be a powerful illusion.

Various experimental attempts have been made to discover how much information on a visual scene is available at any moment in time. Enoch (1959a; 1959b) had subjects search for targets in aerial photographs and found that subjects were biased to search the centre of the image, with efficiency of search decreasing with increasing target eccentricity.

Other, more recent, paradigms have exploited less realistic but more easily analysed stimuli. In such paradigms, the independent variable is the number of items in the display (set size), and the dependent variable is the reaction time. Feature and subsequent conjunction search tasks using such stimuli have illustrated a dichotomous visual search system composed of an early, low-level, parallel system, followed by a later, serial but limited capacity system (Treisman & Gelade, 1980; Julesz & Bergen, 1983).

Change blindness experiments highlight the relative paucity of information that is actually available to influence our visual experience. This research shows that an interrupt in a visual scene (e.g. a blink, a saccade or a blank screen) renders observers blind to significant changes that occur in the scene during the interruption (Mack & Rock, 1998; Rensink, 2000; Simons, 2000). This "change blindness" occurs even when the changes between scenes are significantly large. Change blindness is not a failure to see because of limited visual acuity; rather, it is a failure based on inappropriate attentional guidance. Some parts of the eye and brain are clearly responding differently to the two pictures. Yet,

this does not become part of our visual experience until attention is focused directly on the objects that vary.

The goal of human vision is not to create a replica of the seen world in our heads. A much better metaphor for vision is that of a dynamic and ongoing construction project, where the products being built are short-lived models of the external world that are specifically designed for the current visually guided tasks of the viewer (Egeth & Yantis, 1997; Mack & Rock, 1998; Rensink, 2000; Simons, 2000).

The exact nature of visual search systems remains a lively research topic in cognitive psychology even today, reflecting perhaps, its fundamental importance in describing human perception.

2.2 Theories of Visual Search

For many years vision researchers have been investigating how the human visual system analyses images. There still exists a range of opinions as to the exact mechanisms but most models of selective visual attention since Neisser (1967) and Treisman & Gelade (1980) have included two distinct processes within the search strategy. Neisser distinguished a stage at which simple features are preattentively registered, which determines texture segregation and figure ground grouping, from a second stage at which objects with their complex combinations of features are identified (figure 2.1).

In computational vision (computational models describe vision in terms of an algorithm-like process, taking a macroscopic aspect of human visual ability, e.g. object recognition,

and inventing algorithms to determine if they can explain how humans do it), a similar distinction has been drawn, for example, between Marr's "Primal Sketch" (Marr 1976, 1982) or Barrow & Tenenbaum's "Intrinsic Images" (Barrow & Tenenbaum, 1978) descriptions of early computational vision, both followed by a serial, model-based recognition.

The parallel mechanism was described following the discovery of a limited set of visual properties that are detected very rapidly and accurately by the low-level visual system (Neisser, 1967; Hoffman, 1979; Treisman & Gelade, 1980). This involves a "preattentive" analysis of the visual scene, generally assumed to exploit parallel search capabilities of the visual system, which isolate a target from the distracting background features. These properties were initially termed *preattentive* (Neisser, 1967), since their detection seemed to precede focused attention. We now know that attention plays a critical role in what we see, even at this early stage of vision (Bravo & Nakayama, 1992). The term preattentive continues to be used, however, since it conveys an intuitive notion of the speed and ease with which these properties continue to be identified.

The subsequent mechanism involves the deployment of focused attention to a particular target for detailed image analysis. This search strategy is serial in nature as attention can only be focused on a limited number of image features at any one time and subsequent attention deployment to adjacent image features takes time.

This parallel/serial dichotomy formed the basis for many early theories of visual search but now we know that this strict dichotomy does not exist (Duncan & Humphreys, 1989; Wolfe, 1994a). Instead, visual search appears to be a limited capacity process that involves both parallel and serial mechanisms.

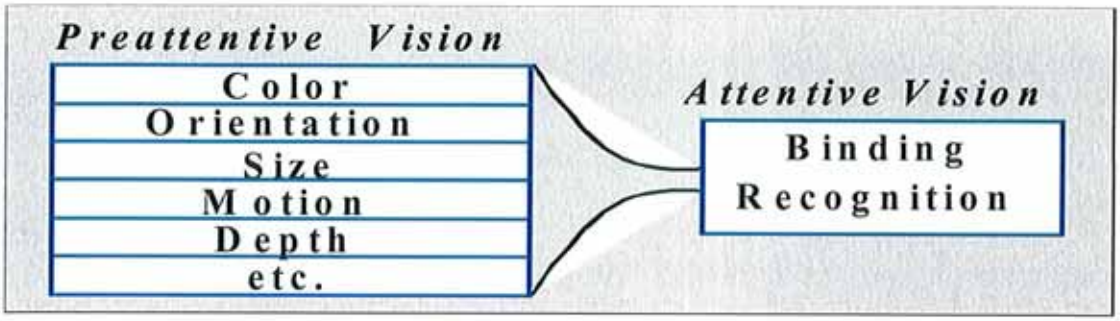


Figure 2.1: Illustration of classic two stage visual search coding features preattentively and using attention to bind image features into recognition. Courtesy J. Wolfe.

2.3 Parallel Search

Imagine yourself running through rough terrain, perhaps fleeing a predator, or perhaps chasing after prey. Your visual system does not have time to scrutinize the countless trees, rocks and other obstacles you may come across. What you need most is enough spatial information to avoid such obstacles, to orient yourself, to pick a path and rapidly detect possible prey.

Extracting spatial layout is a fundamental capacity of biological vision systems. In situations where time and information are limited, an initial, approximate description of the layout of surfaces in the environment can provide crucial information; it can equally serve as a starting point for more detailed object analysis in less constrained conditions. Such capabilities have been labeled as preattentive vision (Treisman & Gelade, 1980).

Preattentive vision is a global visual function that can perform a simple analysis of image content simultaneously across an entire image. Whereas only a single area can be analysed by foveal mechanisms at any one time, preattentive mechanisms can simultaneously

analyse large retinal areas being stimulated by a visual scene (e.g. Flitcroft et al. (1996) exploited pop-out over a thirty degree field). This process is thought to involve parallel processing which allows a very rapid visual search to be performed. During this stage, early visual processes operate across the visual field extracting basic visual features from each item. As the term 'preattentive' implies, this function operates with little or no apparent conscious effort. Preattentively detected stimuli appear to 'pop-out' of a pattern once attention is involuntarily drawn to a stimulus that differs significantly in some basic feature from the surrounding pattern (see Figure 2.2 below).

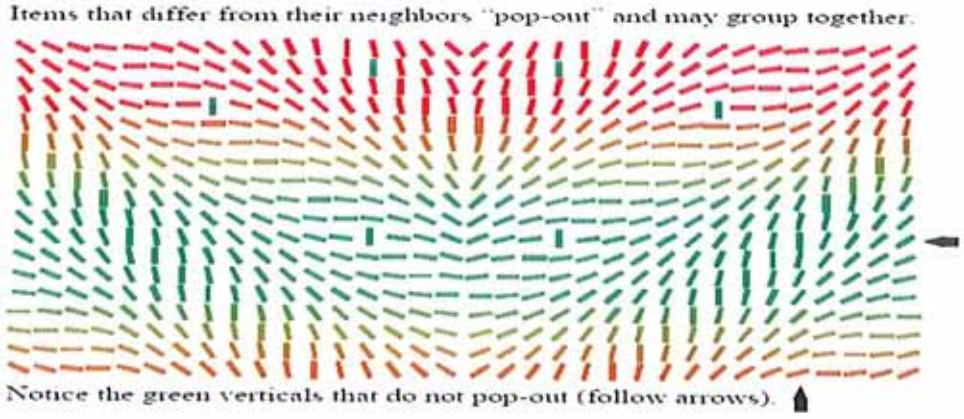


Figure 2.2: The green vertical lines pop out only when surrounding distractors are sufficiently different in some basic stimulus dimension and the line remains the most salient item in the display. The above pop out occurs on the basis of either colour or orientation feature differences. When the feature difference is small, pop out does not occur – follow the black arrows above. Courtesy: J. Wolfe

2.4 Psychological Evidence for Parallel Mechanisms

There are two principal sources of psychological evidence for early visual processing. The first is texture segregation (Figure 2.3), which is likely to reflect early stages of analysis

because it is a prerequisite for figure ground separation that sets up candidates for subsequent object recognition.

Texture segregation and grouping appear to reflect what Julesz (1975) described as immediate, effortless perception, without scrutiny, of distinct areas in the visual field, the initial "parsing" of the world into the objects and backgrounds that may later be identified.

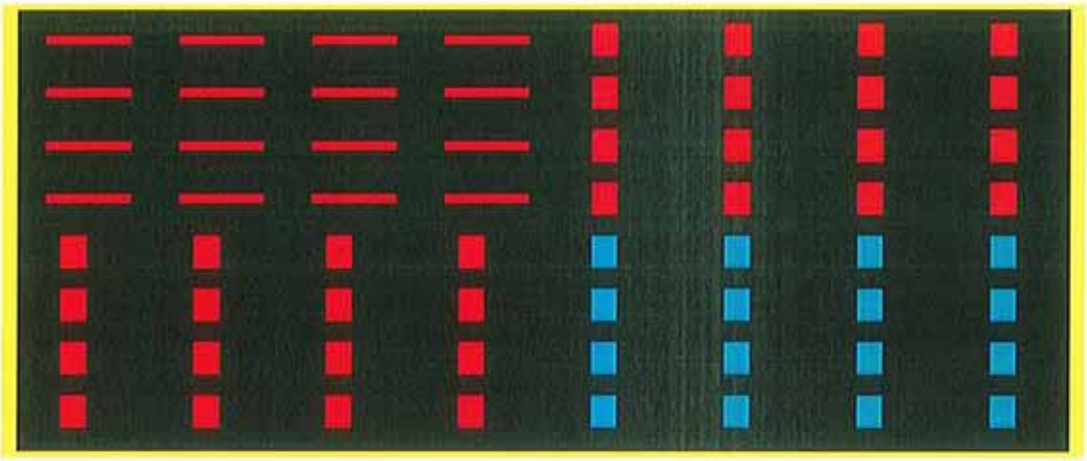
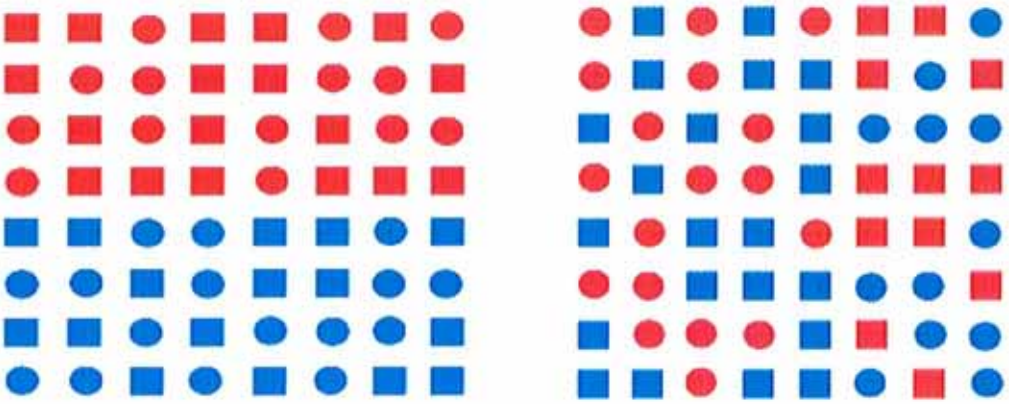


Figure 2.3: Effortless texture segregation for orientation (left) and colour (right). Courtesy J. Wolfe

Beck (1966; 1967), in one of the earliest scientific investigations of attention, showed that texture segregation is easy when it is based on simple properties such as colour (a red area will segregate easily from a blue area – see Figure 2.3); brightness (a dark area will segregate easily from a light one); and line orientation (an area containing tilted T's segregates well from an area containing vertical T's). However, if two areas differ only in line arrangements (one contains T's and the other L's), the boundary becomes more difficult to detect.

Boundaries defined by conjunctions of features (e.g. red circles and blue squares on one side, and red squares and blue circles on the other – see Figure 2.4) are also more difficult to locate.



(a) (b)

Figure 2.4: An example of a boundary detection task from Treisman's experiments: (a) a boundary defined by a unique feature such as hue (red circles and red squares on the top, blue circles and blue squares on the bottom) is preattentively classified as horizontal; (b) a boundary defined by a conjunction of features (red circles and blue squares on the left, blue circles and red squares on the right) cannot be preattentively classified as vertical (Treisman & Gelade, 1980; Treisman, 1985)

Beck (1967) suggested that texture segregation depends on features that are easily discriminable with peripheral vision and with distributed attention. More recently, Beck (1982) also suggested that texture segregation results from a computation of local differences, which is performed automatically across the visual field. Any discontinuity where adjacent elements differ in one or more features sets up a boundary between adjacent regions.

Texture segregation is readily apparent in natural visual scenes, for example, the appearance of the horizon, alterations in colour and shading from clouds over mountains etc – (see Figure 2.5 for examples of natural texture segregation).

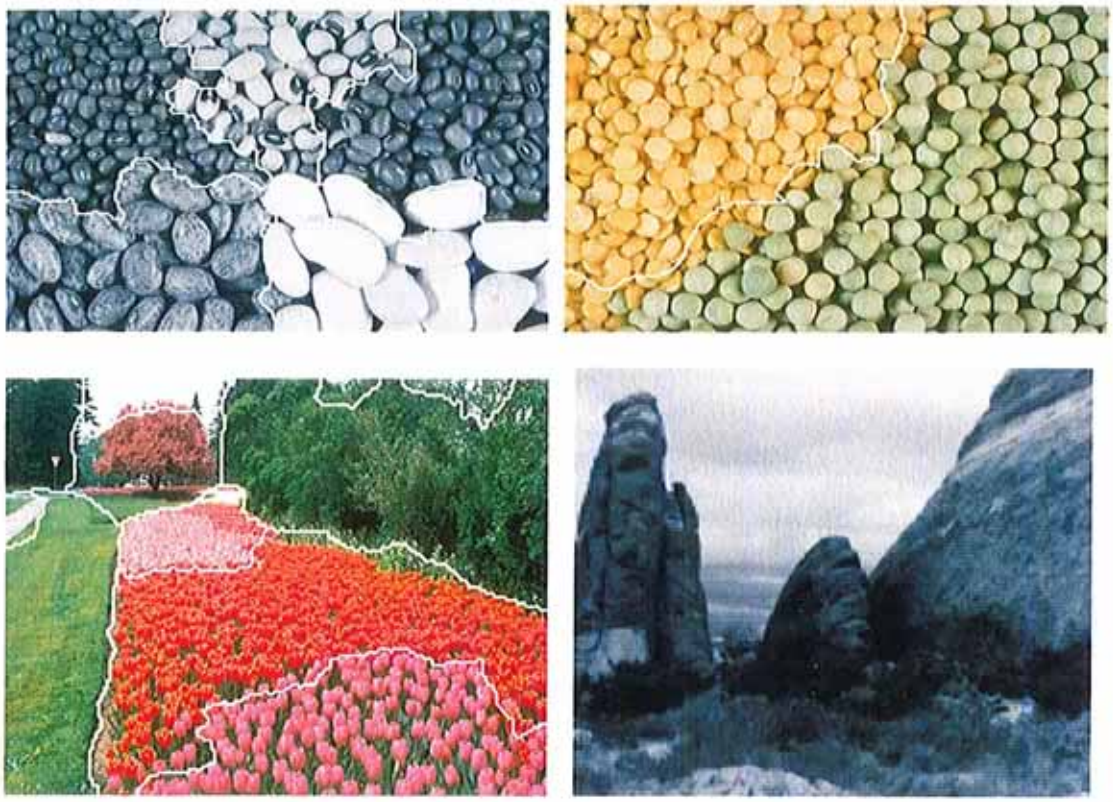


Figure 2.5: Natural texture segregation facilitating effortless boundary detection. From: www.cs.indiana.edu/.../ Hucka/natural.gif & http://vision.ece.ucsb.edu/.../ images/garden_edge.gif

The second source of psychological evidence for early visual processing comes from experiments on visual search. Countless studies have shown that the search for a target pattern among distractor (non-target) patterns is fast and parallel (i.e. the search time is almost independent of the number of distractors in the display), when the difference between the target and distractor patterns in some basic stimulus dimension is big enough-

(e.g. Treisman & Gelade, 1980; Nakayama & Silverman, 1986; Treisman & Gormican, 1988; Wolfe, 1992a; Verghese & Nakayama, 1994; Wolfe, 1994a).

Items for which search is parallel are considered to contain elementary features which are processed preattentively. These features are thought of as the building blocks of visual perception. Examples of such features are – colour, size, luminance, motion direction, orientation, convergence, closure of lines, contrast, and others (see Table 2a). For instance, when there is a large spatial frequency, colour or orientation difference between a target and distractors, the search for the target takes place rapidly and in parallel, the target 'pops-out' among the distractors, being immediately detectable as the target, requiring no foveal attention. Carrasco et al. (2003) have shown that the periphery is actually more efficient at rapid visual processing than the fovea, although reaction times and error rates tend to be lowest for targets closer to fixation because of the attentional bias to central vision (Cheal & Lyon, 1992; Sekuler & Ball, 1986).

2.5 Table 2a – Preattentive Features

PREATTENTIVE FEATURE	RESEARCH STUDY
LINE (BLOB) ORIENTATION	Sagi & Julesz (1985a)
LENGTH	Treisman & Gormican (1988)
WIDTH	Sagi & Julesz (1985b)
SIZE	Treisman & Gelade (1980)
CURVATURE	Treisman & Gormican (1988)
NUMBER	Sagi & Julesz (1985b); Healey et al. (1993); Trick & Pylyshyn (1994)
TERMINATORS	Julesz & Bergen (1983)
INTERSECTION	Julesz & Bergen (1983)
CLOSURE	Enns (1986); Treisman & Souther (1986)
COLOUR (HUE)	Nagy & Sanchez(1990);Bauer et al. (1996); Bauer et al. (1998); Healey & Enns (1999)
INTENSITY	Beck et al. (1983); Treisman & Gormican (1988)
FLICKER	Julesz (1971)
DIRECTION OF MOTION	Driver et al. (1992)
BINOCULAR LUSTRE	Wolfe & Franzel (1988)
STEREOSCOPIC DEPTH	Nakayama & Silverman (1986)
3D DEPTH CUES	Enns (1990b)
3D ORIENTATION	Enns & Rensink (1990a); Liu et al. (2003)
LIGHTING DIRECTION	Enns (1990a)

A glance at Table 2a and Figure 2.7 illustrates that while there are some obvious candidates for preattentive processing such as colour and motion, there are also some less obvious properties such as lustre and 3D depth cues that are also processed in parallel. These less basic "basic features" illustrate an important point. Parallel processing of visual information extends beyond early vision to a level that handles more complex properties of surfaces and their relationship to one another (He & Nakayama 1992, & 1994). For example, several authors have shown (using stimuli similar to that in Figure 2.6) that preattentive visual processes "understand" occlusion and correctly assign ownership of edges to occluding and occluded objects (Enns & Rensink, 1992 & 1998; Wolfe 1998a). Occlusion would pose difficulties for a visual search mechanism that only had access to simple features.

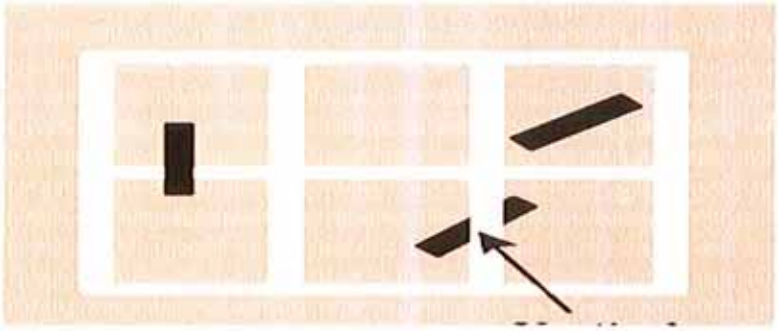


Figure 2.6: Occlusion is "understood" by the visual system so it is not fooled by the white vertical line indicated by the arrow. (From: Wolfe, 1998a).

Further evidence that visual search uses relatively "late" parallel representations comes from experiments that show that "basic features" in visual search can be built up of primitives from other feature spaces such as oriented items defined by colour, texture, motion etc. (Bravo & Blake, 1990; Cavanagh et al., 1990).

These findings, together with many others suggest that preattentive processes have access to conjunctions of features, and in fact have already done some of the

segmentation and integration of features that are necessary to guide attention and possibly even form object recognitions.

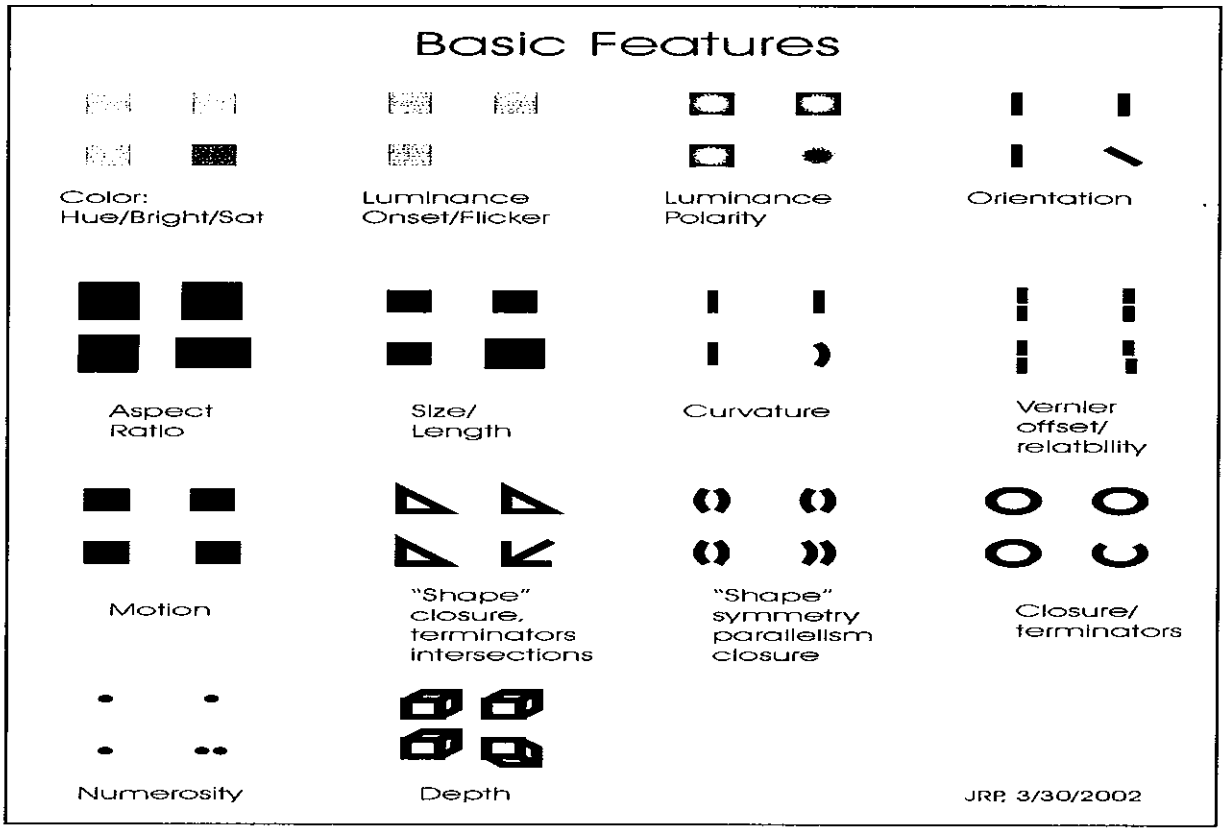


Figure 2.7 – Illustration of Potential Preattentive (Basic) Features. From: www.owlnet.rice.edu/.../ Images/BasicFeatures.gif

Typically, tasks that can be performed on large multi-element displays where reaction times and error rates remain unaffected by set size are considered preattentive (McElree & Carrasco, 1999). Reaction time based paradigms illustrate shallow (near zero) reaction time slopes for variations in set size (parallel search time <10msec per additional set item, serial search times are > 20mecs per additional set item - Treisman, 1985), while speed-accuracy trade-off paradigms show no accuracy effects with set size increases at fixed display times (<200msecs). Eye movements take at least 200 milliseconds to initiate (Yang et al., 2002), and random locations of the elements in the display ensure that attention cannot be pre-focused on any particular location, yet

viewers consistently locate such elementary feature targets with very little effort. This suggests that certain information is processed in parallel by the low-level visual system. More detailed tasks require focused attention and therefore reaction time will increase linearly as the number of distractors increases due to required changes in fixation. Error rates will also increase for fixed display times eventually reaching accuracy levels facilitated by chance for larger set sizes (McElree & Carrasco, 1999).

Figure 2.8 below illustrates efficient search in both feature and conjunction tasks. There is no increase in reaction time with increasing numbers of distractors in feature search in a + b. The linear slope increase in (c) indicates the search for the target (pink vertical line) is more difficult. Such conjunction targets are a special case as the search is still too efficient to be termed serial (RT < 20-40msecs per distractor – Treisman, 1985; Wolfe, 1994a). See Guided Search theory (section 2.13) later for a comprehensive discussion of such effects.

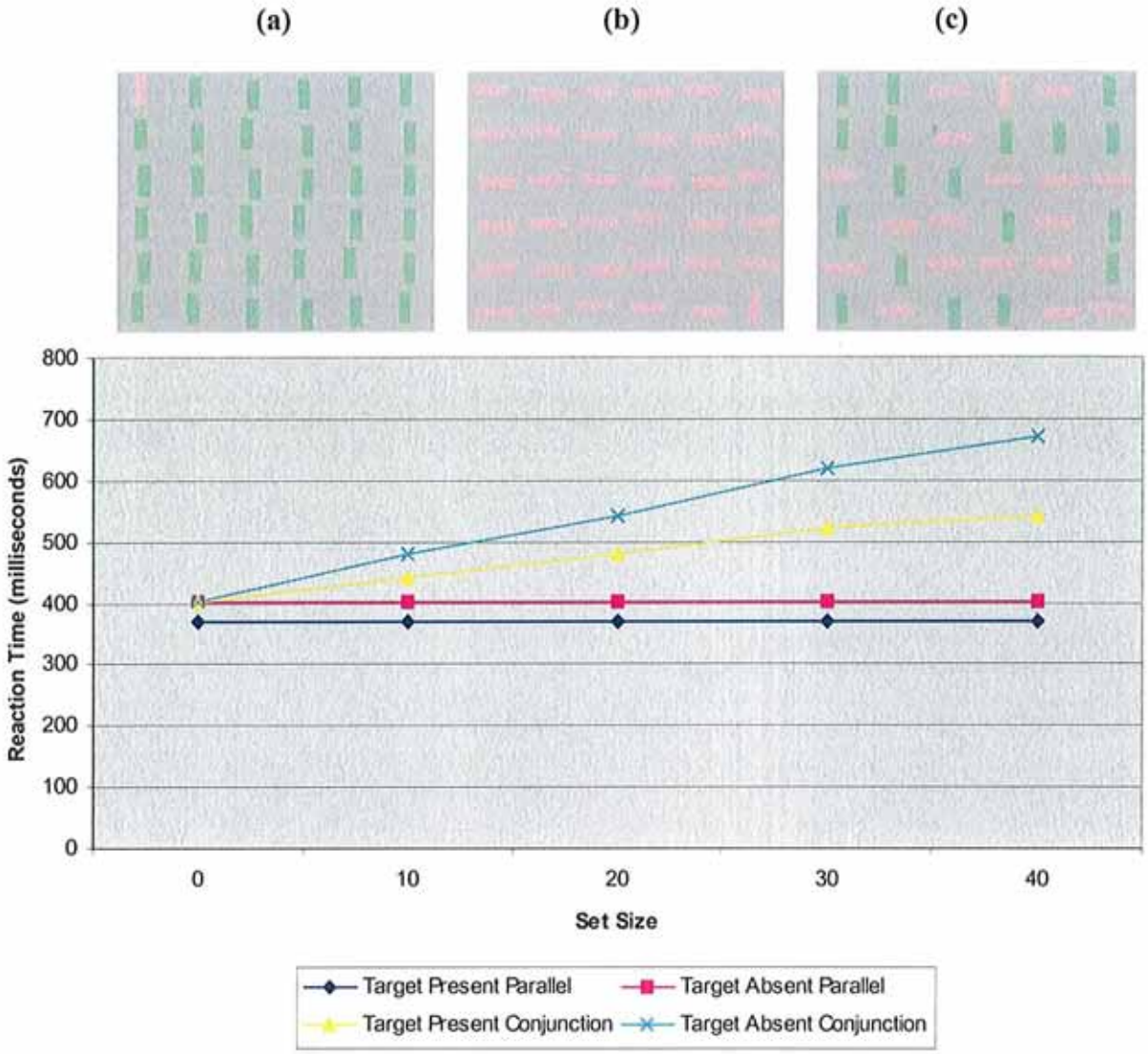


Figure 2.8: Illustration of parallel search for colour or orientation feature difference (a + b) and (c) colour/orientation conjunction task above. From: http://www.vrlab.uci.edu/dzmura/images/csdemo/csdemo5.gif

2.6 Physiological Evidence for Parallel Mechanisms

Physiological evidence has accumulated demonstrating that early stages of visual processing are analytical, that is, that they decompose the physical array of light along a number of separate dimensions (e.g. Figure 2.9). Not alone are such features processed along separate pathways, they also seem to be mapped into different areas of the brain, each of which is specialized to analyse a different property; for example,

neural units selectively responsive to particular orientations are found in one area (although there is some overlap), those responsive to stereo depth in another, those to colour, movement and so on in yet other functionally separate areas (Cowey 1979; Hubel & Wiesel 1968; Zeki, 1981; Maunsell & Newsome, 1987).

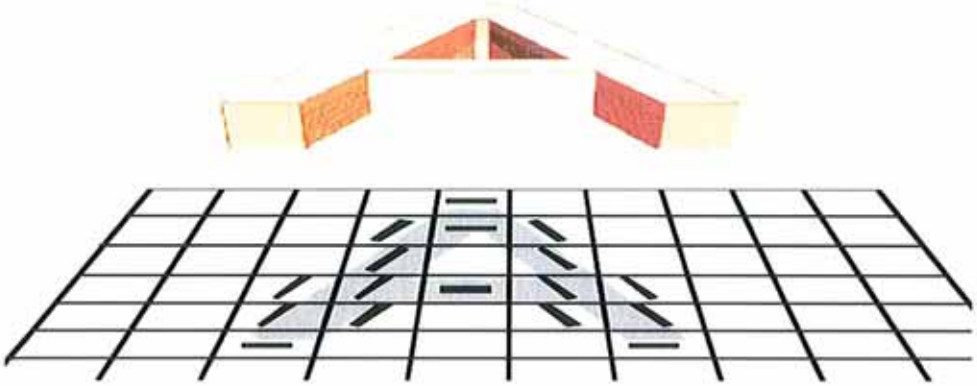


Figure 2.9: A feature map for orientation given the letter "A" as an input. The visual system breaks the image down into its component orientations. Dark bars in each cell indicate the computed local orientation for that position. The shadow of the "A" is provided for clarity and is not part of the feature map.

Recorded VEP's have also been used to analyse processing systems. Towle et al. (1980) showed that different tasks, requiring different levels of discrimination, have different evoked response latencies. One can infer from this that some object properties are extracted before others. Such differences in processing time may supplement the above-mentioned differences in the localisation of feature processing, as evidence for specialized analysis.

One can also demonstrate adaptation that is selective to specific properties. For example, if one stares at a waterfall and then looks at the bank, it appears to flow in the opposite direction (waterfall illusion). This may reflect selective adaptation of detectors for a particular direction of movement, which respond independently of what

is moving. The bank looks very different from the water in terms of colour and texture, but it still shows the aftereffects of movement.

Mach bands are another illustration of this adaptation, illustrating selective spatial filtering performed by specific cells, which can be taken as evidence of selective sensitivity of cells to certain spatial frequencies.

Rather than consisting of a single channel, maximally sensitive to a spatial frequency of 4 cycles/degree (Figure 2.10), the human contrast sensitivity function (CSF) can be thought of as an envelope that encompasses numerous, more narrow, independent channels (Figure 2.11 (left) - Blakemore & Campbell, 1969).

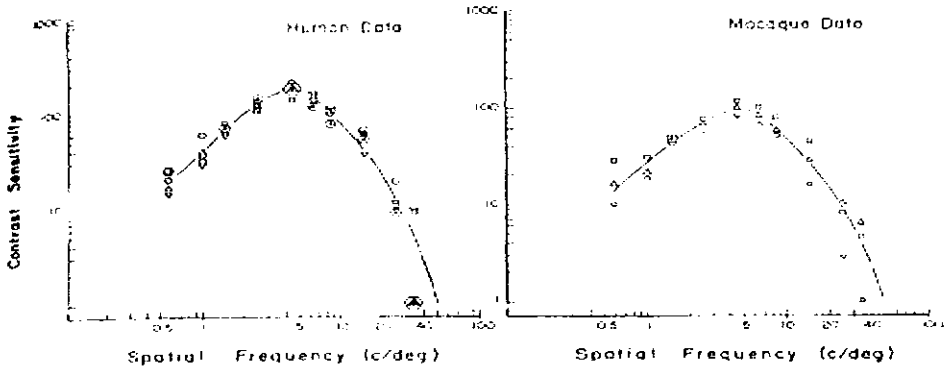


Figure 2.10: Contrast Sensitivity Function of the visual system showing peak sensitivity at 4cpd. After: Blakemore & Campbell (1969).

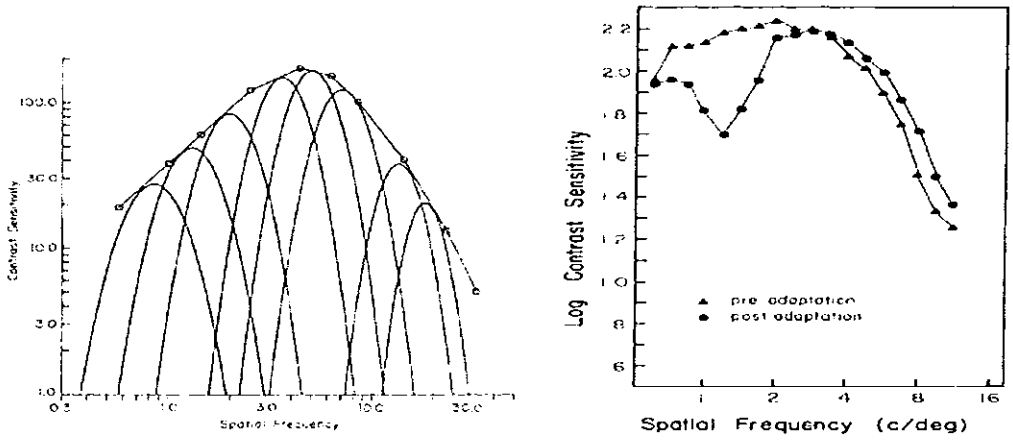


Figure 2.11: Selective spatial frequency channels (left) and evidence of selective spatial frequency sensitivity (right) After: Blakemore & Campbell (1969). Figs. 2.10- 2.11 from: http://mathcs.holycross.edu/~croyden/vision/notes/Lecture11.ppt

Psychological experimental evidence exists for different channels responding to different values within a single sensory domain. A well-known example of this is the evidence that different spatial frequencies are signalled in different channels. Blakemore & Campbell (1969) studied the effects of spatial frequency adaptation of the human contrast sensitivity function (CSF). A subjects' CSF was measured, the subject was then adapted to a specific spatial frequency, and the CSF was then re-plotted. The second CSF plot exhibits a discrete reduction in sensitivity only at the spatial frequency to which the subject was adapted, rather than across all spatial frequencies, which would be expected to occur if there was only one spatial frequency channel – see Figure 2.11 (right).

Blakemore and Campbell (1969) also demonstrated that a subject adapted to a square wave grating with a specific spatial frequency exhibits reduced sensitivity, not alone, to the fundamental frequency, but also to the third harmonic frequency.

Thus it appears as though the visual system is capable a breaking down the complex square wave stimulus into its basic spatial frequency components (a fundamental and its harmonics), which may represent some form of Fourier analysis by the visual system (Schwartz, 1994).

It has been hypothesised that visual perception results from two-stage processing of sensory information: a rapid parallel stage followed by a slower serial stage. Such a model can be tested by monitoring the recognition process for each item in a display throughout a trial with an observer searching for a particular target. We would expect to see that, initially, in a target-absent display, with all display items equally dissimilar to the search target, all the objects in the display would be processed in parallel, but in subsequent displays, as the similarity of a single item to the target started to exceed that of the distractors, attention would be shifted to the similar targets position, and processing of distractors would decline.

Observations very close to these predictions were reported by Chelazzi et al. (1993). They recorded activity of cells in the inferior temporal (IT) area of monkeys in response to complex shapes. This is an area that appears to be important for recognizing objects and receives its principal input from the extrastriate visual areas whose cells seem to be concerned with fairly simple features such as line orientation, colour etc.

For each cell, they found a shape that activated the cell and another that had no effect. Each of these shapes then served as targets in a visual search task. The monkey was rewarded for moving her eyes to the appropriate target as quickly as possible. The monkey initially fixates the display. Following fixation, a cue object (e.g. the triangle in figure 2.12) is presented, followed by a display of the two objects.

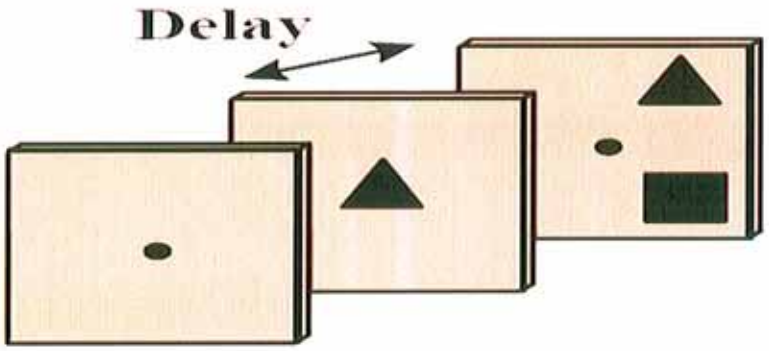


Figure 2.12: Sequence of trial events in the Chelazzi et al. study. A fixation point is followed by a cue stimulus. Following a delay, the array is presented and the monkey makes a saccade to the location whose shape matches the cue.

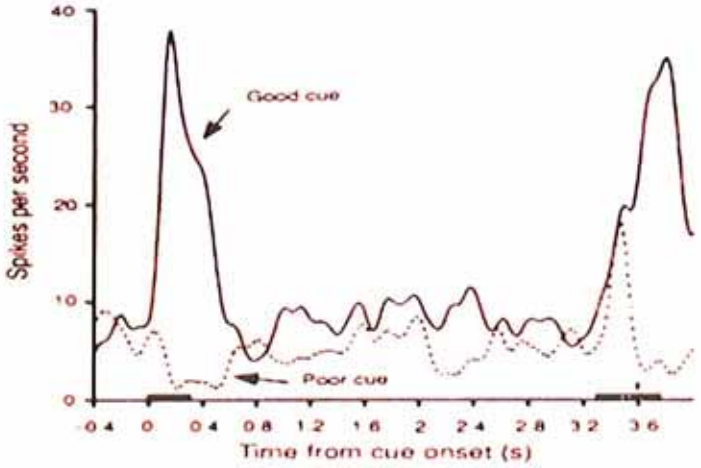


Figure 2.13: Results of the Chelazzi et al. study. The curve labeled "good cue" represents the response of a cell tuned to the target, that labeled ("poor cue") represents the response of a cell tuned to the distractor. From: Chelazzi et al. (1993).

In Figure 2.13 the curve labeled "good cue" shows the activity of cells that respond to the target shape (triangle), and that labeled "poor cue" shows the activity of the cells responding to the rectangle. The solid bars on the time line show the onset of the cue object and, following a delay, the onset of the array.

Following the cue, cells that respond to the triangle become activated, and remain activated in the interval before the array onset, as top-down mechanisms intervene as if the monkey is holding in mind the target representation of a triangle. Shortly after the onset of the array, cells responding to both objects in the display become active, as preattentive mechanisms rapidly extract both object features and make representations in the relevant feature processing locations. However, the activity of the non-target cells quickly returns to baseline while target cell activity continues to grow.

This is precisely the pattern we would expect if search starts with a parallel recognition of all the display objects and is followed by attention to the target and tends to provide some basic physiological evidence for a dual search system, although offering little insight into the processing of more complex visual scenes.

In the opening paragraph, parallel processing is described as a search strategy using bottom-up, stimulus driven information. Bottom-up activation, based on local feature differences alone can be sufficient to guide attention to a target location. Nakayama (1999) considers the pop-out phenomenon to be a physiological process involving the involuntary jerking of attention to an "odd" item. The strength of bottom-up activation is based on the magnitude of the difference between an item and its neighbours. The identity of more remote items is less important. If the difference is large enough, attention will be guided to the target which pops out immediately on every trial and reaction time will be independent of the number of distracting features in the display.

Different features appear to have different abilities to attract attention, with abrupt onset and/or the creation of new objects being, perhaps, the most forceful. However it is important to recognize that a system used to guide attention that was entirely

stimulus driven would not be particularly useful. It is important to be able to guide attention toward currently relevant features in the visual input. Otherwise, a more salient, flashing neon sign might continuously disrupt the search for a coin dropped on the pavement.

It is obvious that people can, and must, bring search under volitional control, although our ability to command parallel processing is limited. This is demonstrated by an inability to search in parallel for targets that do not lend themselves easily to bottom-up detection, for example, the detection of targets defined by certain conjunctions of more than one feature. The mechanics of parallel search will be explored in more detail later.

2.7 Asymmetry in Parallel Search

The traditional idea that a target will pop-out from the distracting background once it differs significantly from the background in some basic feature dimension needs qualification based on the observation that feature searches appear to be asymmetric (see Figures 2.14 & 2.15). That is, the search for target *x* among distractors *y* does not yield the same result as a search for target *y* among *x*'s. Such asymmetries have been widely reported for feature searches involving colour, motion and orientation.

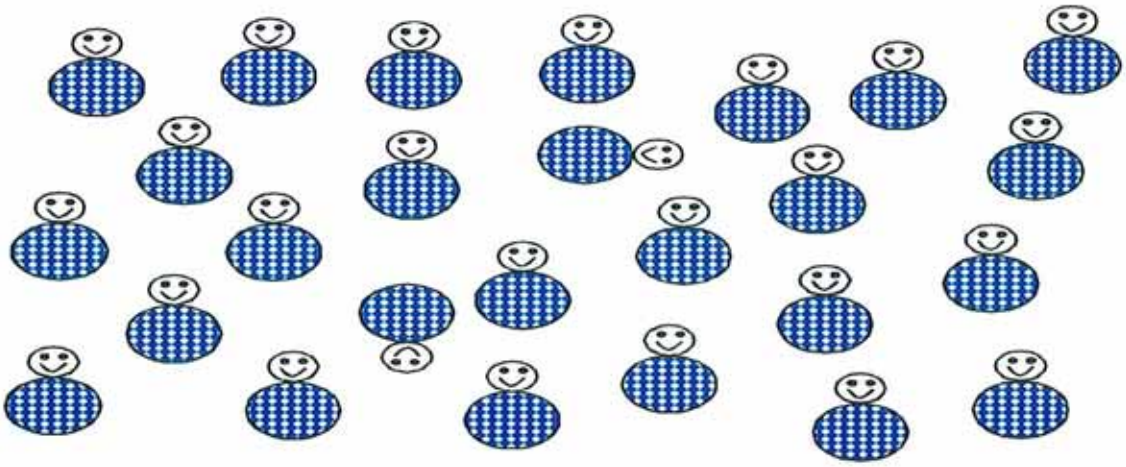


Figure 2.14: – the 90-degree target is instinctively easier to locate even though both targets are distinctly different from the surrounding distractors. Courtesy J. Wolfe.

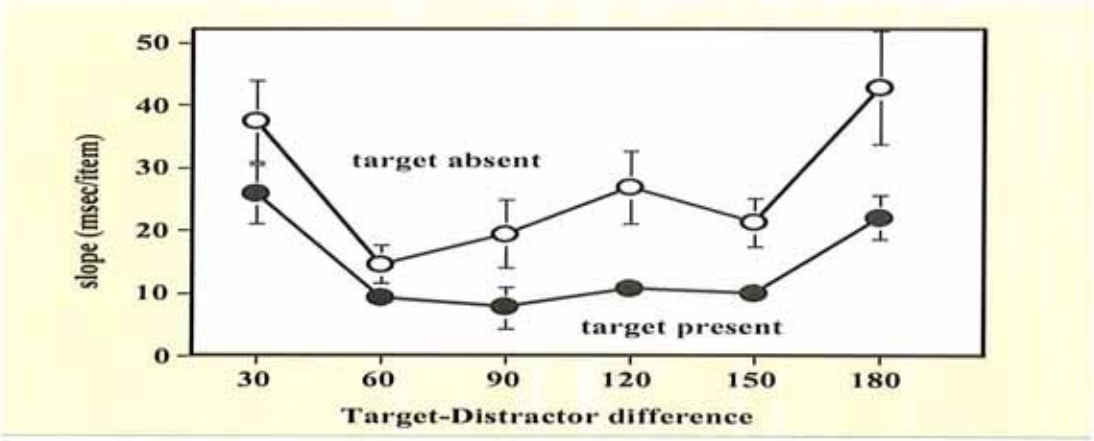


Figure 2.15: – the 90 degree target exhibits the lowest search time (msec/item), with the 180 degree target distinctly more difficult and requiring more than double the time to locate. Courtesy J. Wolfe.

In orientation, for example, symmetric search results would show pop-out for a vertical line target among tilted line distractors and also pop-out of a tilted line when surrounded by vertical distractors, in other words, the search for both types of stimuli should be equally efficient given that the feature difference is identical. Treisman has found (Treisman & Souther 1985; Treisman & Gormican 1988), and many have replicated, that it is easier to search for a tilted line among vertical lines than vice

versa. Such asymmetries have given valuable insight into the basic features of visual processing. Treisman was the first to argue (Treisman & Gormican, 1988) that search asymmetry is one mark of a basic, preattentive feature. Specifically, this infers that it would be easier to search for a target defined by the presence of a basic feature rather than one defined by its absence (see Figure 2.16).

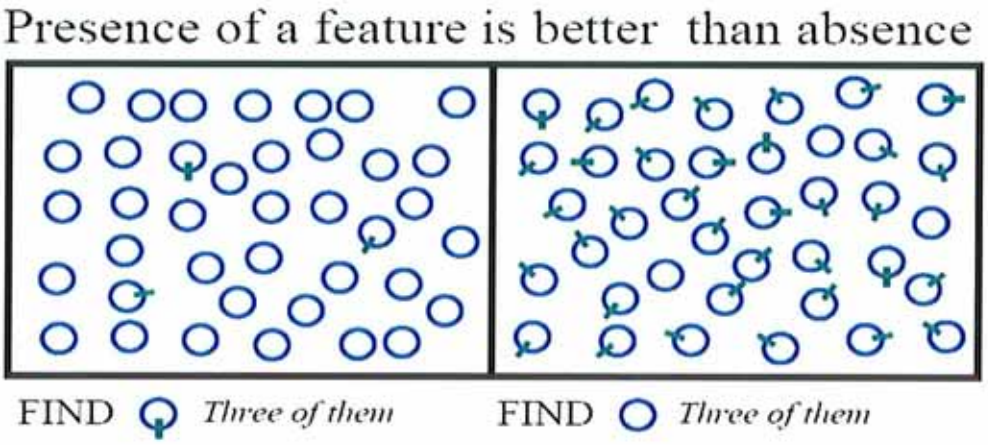


Figure 2.16: It is easier to find the circles with the vertical line among plain circles than vice versa. The presence of the line above adds at least four candidate basic features to facilitate the rapid detection on the left: orientation, size/length, intersection and line termination. The absence of the features on the right means these stimuli are more difficult to locate. Courtesy J. Wolfe

Treisman also proposed that if one item has more of a feature than another, then the search for the target with more among the items with less will be more efficient than the search for the item with less among more. Thus, the search for long lines (more) among short lines (less) is more efficient than the reverse.

She also proposes that it is easier to find deviations among canonical stimuli (stimuli which the system is highly tuned to or familiar with) than vice versa. This would explain the orientation asymmetry outlined above with the vertical line being the canonical stimulus. Wolfe (1998a) explains this orientation asymmetry somewhat

differently but with more or less the same conclusion. Orientation is categorised as degrees of rightness or leftness for preattentive purposes. The tilted target above (figure 2.16) has the basic "rightness" feature and therefore easier to detect than a target defined by the vertical which has no tilt.

2.8 Role of Familiarity and Novelty in Search Asymmetry

An extension to Treisman's hypothesis, that it is easier to detect a deviant from among standard stimuli than to find the standard among deviants (see Figure 2.17), is the proposition that deviation or "novelty" per se has preattentive status as a feature (Wang, Cavanagh & Green, 1994). That is, novelty might be a feature such as colour or size, though perhaps slightly weaker in its ability to support efficient search.

Based on Treisman's hypothesis, "familiarity" would be the canonical stimulus and "novelty" would pop-out as the deviant. The claim that familiarity/novelty can be processed preattentively is important, because it again implies parallel processing of letter stimuli to a level of recognition adequate for one to distinguish novel letters from familiar. This would contradict "early selection" accounts that hold that attention is required for object recognition (Wolfe, 1994a).

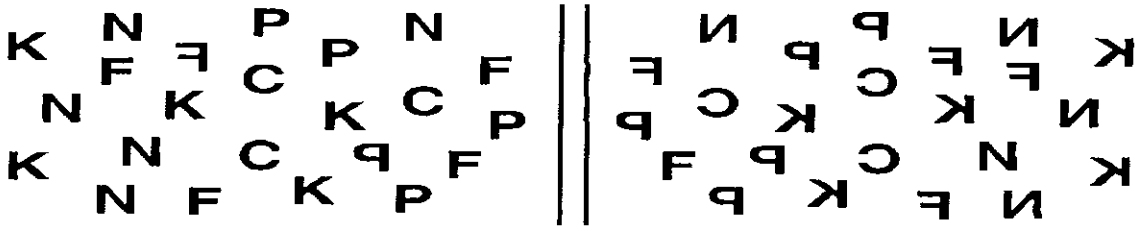


Figure 2.17: In each panel there are two targets. On the left they are mirror-reversed letters surrounded by letters in their normal orientation, on the right they are normal letters surrounded by mirror-reversed letters. The standard finding is that it is easier to find the mirror-reversed letters, which are essentially novel or unfamiliar shapes. (From: Wolfe, 2001).

Experimental data strongly argue for the importance of the familiarity of the distractors. Shen and Reingold (2001) showed that search was more efficient when the distractors were familiar. They performed an intriguing experiment using stimuli familiar to subjects with knowledge of the Chinese language (see Figure 2.18).

Chinese subjects found the "novel" target on the right, when surrounded by the familiar distractor, easier to find. Interestingly however, subjects unfamiliar with both stimulus types find the target on the left easier to locate. Even more interesting is the fact that such subjects are actually faster and more efficient at this search task than the Chinese subjects. Apparently, they can exploit the basic orientation difference to drive the search, and are unaffected by the stimulus meaning.

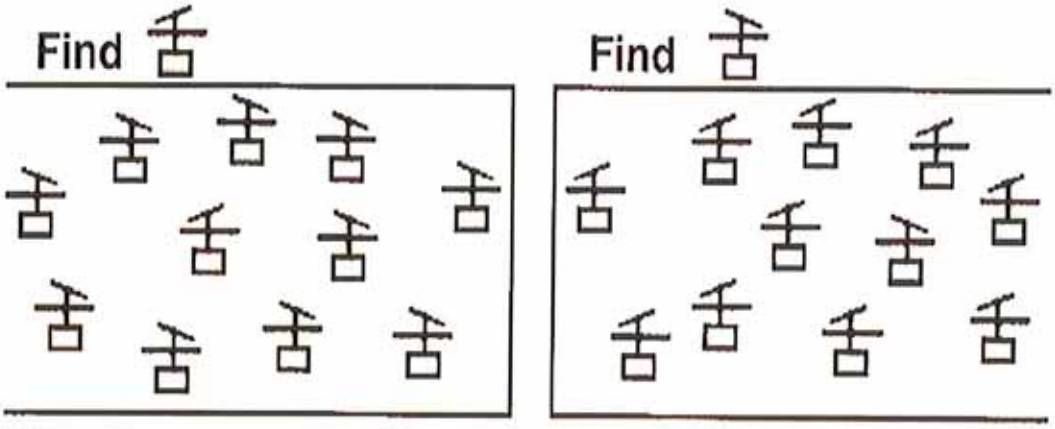


Figure 2.18: If you are not familiar with the Chinese language, then the search target on the left (which means "tongue") when surrounded by the mirror-reverse image (which is meaningless) is easier. If however you are Chinese, the search for the novel target on the right proves easier than the search for the "familiar" tongue ideogram on the left. From: (Shen & Reingold, 2001; Wolfe, 2001)

Other experimental results indicate that the effect of familiarity is not confined to just letters and illustrate that the effects of familiarity are quite general. Stimuli consisting of upright versus inverted faces, or upright "live" versus inverted "dead" animal silhouettes demonstrate the same familiarity/novelty effects. The novel (inverted) face or animal shape is easiest to locate when surrounded by the stimulus in its familiar orientation (Figures 2.19).

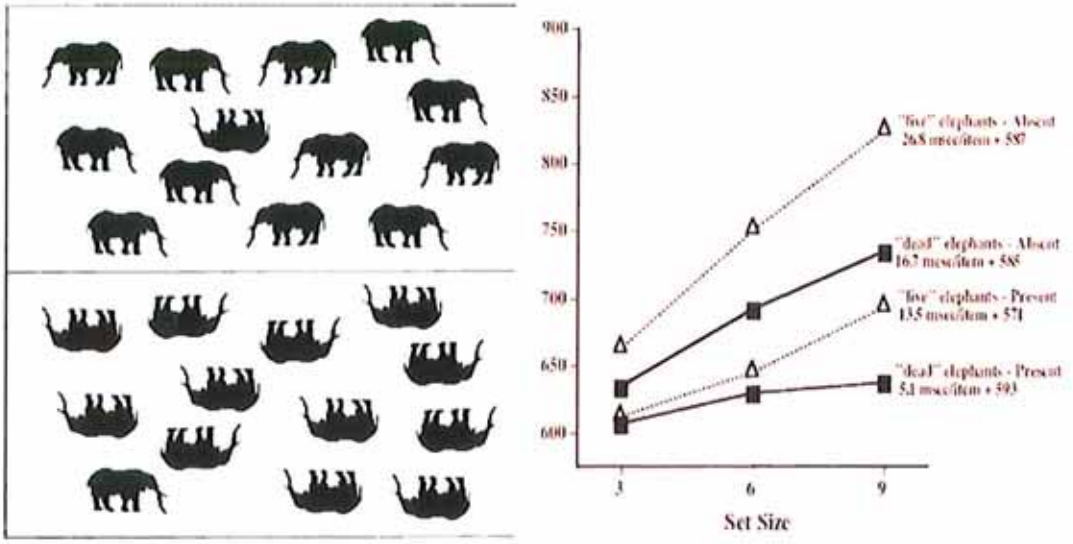


Figure 2.19: Find the "dead" elephant on top or the "live" elephant on the bottom. Search for a dead elephant is very efficient, but somewhat less efficient for a live elephant. From: Wolfe, (2001).

Extensive work remains to be done in the area of search asymmetry, but despite the puzzles and complications arising from it, it continues to yield clues and point toward a clearer understanding of preattentive processing.

2.9 Serial Search

"What a piece of work is man, how noble in reason, how infinite in faculties…"

(Shakespeare: Hamlet, 2:2:312-313)

Hamlet was wrong! We are dramatically limited in our faculties. Perhaps, if preattentive mechanisms represented the "be all and end all" of our visual search faculties then this might be true in terms of vision. The goal of preattentive processing is merely to extract a preattentive representation from the stimulus that can be used to guide attention. It would be a mistake to think of this representation as self-sufficient "preattentive vision" whose output can directly control behaviour. While some forms of perceptual grouping and segregation may be accomplished preattentively, it does not seem routinely possible to go directly to a motor response, except possibly in terms of a reflex response to threatening stimuli.

While preattentive mechanisms can extract basic features from a scene, complex stimuli like faces and words can only be identified one at a time. Attention must be deployed to an item before it can be fully identified. Somewhat informally, serial processing means strictly sequential, without overlap of the successive processing times on objects or distinct subsystems. In a standard type of serial system, each object takes the same average amount of time to process and processing of subsequent objects begins only when the previous one is completed.

In terms of modern experimental methods, the limited capacity of serial search systems means that, as the complexity of the visual scene increases, the search time required to locate a target increases. The traditional method of exploring reaction times in response to increasing set size produces a phenomenon of linear increasing reaction time curves when the target does not exhibit any single defining elementary feature difference from the distracting background (see Figure 2.20). The search for such a target proceeds without preattentive guidance and produces approximate target-present slopes of 20-30 milliseconds per item in the display (40-60 milliseconds for target-

absent displays). Such data are roughly consistent with a serial, self-terminating search; although there are limited-capacity parallel accounts of the same data (Palmer, 1995; Townsend, 1990) so cannot be taken as concrete evidence of a serial search strategy.

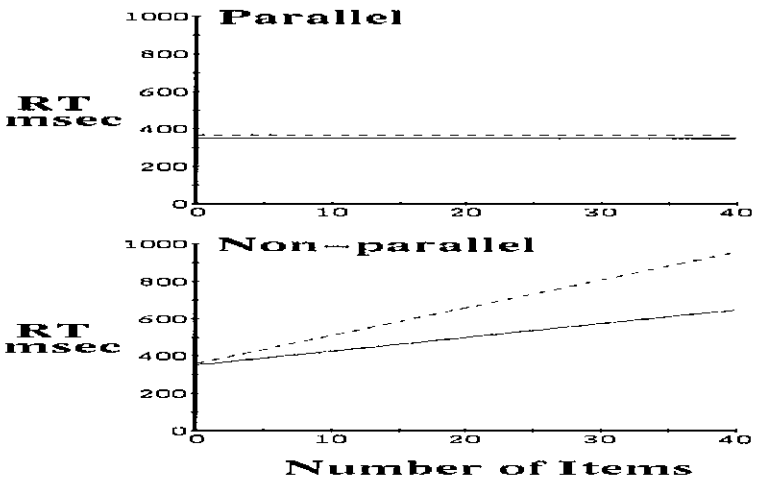


Figure 2.20: Reaction time slopes for serial and parallel search for target present (solid line) and target-absent (dashed line) trials. Courtesy J. Wolfe.

Whatever mechanism, whether serial or limited capacity parallel, such set size effects do illustrate that some process involved in search either has a limited capacity so that objects in the display need to be examined one at a time (i.e. serially), or at least one that becomes less efficient with increasing load.

There is wide agreement on the presence of bottlenecks in human information processing (Neisser, 1967). Humans cannot handle all of the demands placed on them at the same time. Shakespeare observed as much when in "As You Like It", Celia meets Orlando in the woods. When Rosalind, who loves Orlando, asks Celia for information about this meeting, she gives instructions for response comparable to the most arduous laboratory attention tasks:

"*What did he when thou saw'st him? What said he? How looked he? Wherin went he? What makes he here? Where remains he? How parted he with thee? And when shalt thou see him again? Answer me in one word.*" (As You Like It 3.2.223-224)

Celia, described humorously by Wolfe (1994b) as a "paleocognitive scientist", recognizes a bottleneck and responds

"*you must borrow me Gargantua's mouth first; tis a word too great for any mouth of this age's size*" (As You Like It, 3.2. 223-224)

Parallel Processing Bottleneck Object Recognition

Figure 2.21: Before objects can be recognized, limited capacity serial attention must be deployed creating the characteristic bottleneck which slows down visual performance. Courtesy J. Wolfe.

The study of visual processing has provided the clearest examples of processing bottlenecks. The initial stages of visual processing are spatially parallel. At some stage in the journey from image to perception and action, however, there is a bottleneck (Figures 2.21 + 2.22).

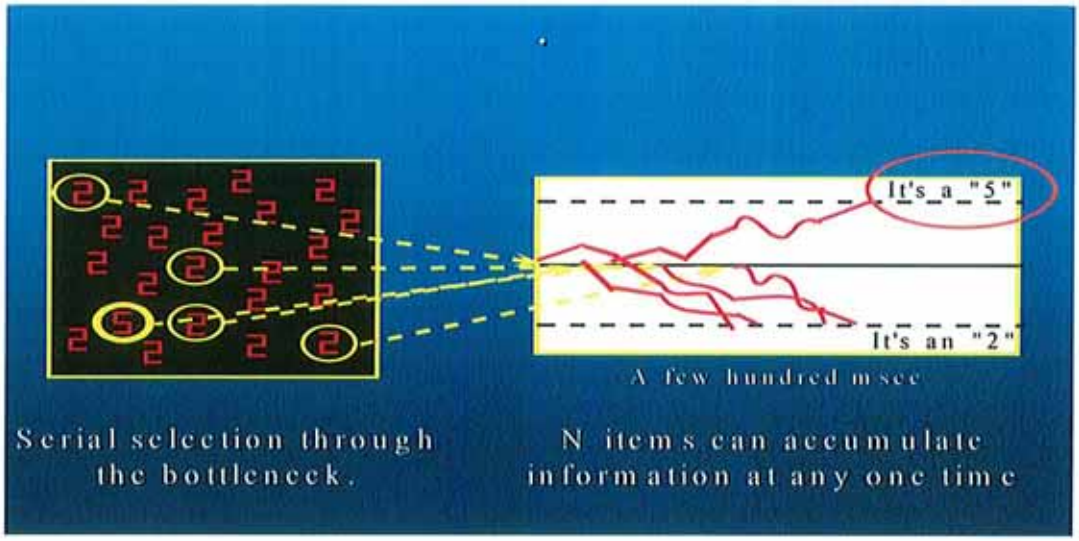


Figure 2.22: Serial search can be likened to an asynchronous diffusion of display items through a bottleneck that limits the amount of information that can be accumulated at any one time, resulting in characteristic set size effects. Courtesy J. Wolfe.

Attention selects some stimuli for more processing than others and this processing takes place serially, item by item taking more time, possibly up to 40-60 milliseconds per item (Wolfe, 1994a). In any visually complex scene it is clear that such serial processing could be potentially crippling, where it could take several seconds to process a scene that might require a much shorter response time. Most searches in the real world do not take so long to process; some items and loci are processed before the bottleneck. Such rapid attentional deployment to visually important stimuli requires intricate interaction between both parallel and serial mechanisms. The precise mechanisms of such interactions have been the subject of intense scrutiny and have led to the formulation of two rival sets of theories of visual search.

2.9.1 Combining Features

Beyond visual search tasks, there is the more general question of how disparate features within a given object are combined to form a coherent percept. While preattentive features are extracted in parallel, such features cannot be bound to facilitate object recognition without serial attention.

Supporting evidence for such a hypothesis comes from the discovery of illusory conjunctions (Treisman & Schmidt, 1982; Cohen & Ivry, 1989). Imagine very briefly viewing a display containing a green "X", a red "S" and a yellow " | " adjacent to each other. Observers often report seeing *illusory conjunctions* of features, for instance, a red "X" or green "S".

Apparently, without the benefit of time to allocate serial attention, features corresponding to a given spatial location are not bound together, that is, they may be combined incorrectly.

Such binding together of features across preattentive maps (see discussion of Feature Integration – section 2.10 and Guided Search – section 2.13 theories) is one of the primary functions of serial attention (Treisman & Gormican, 1988; Wolfe, 1994a).

Following the perceptual organisation of visual input, the layout of the scene is represented as a collection of coherent surfaces and objects. Indeed there are many situations in which this representation may be sufficient for successful task completion. For example, navigating a hallway may only require detection of obstacles; likewise, grasping an object may only require noting its size and rough shape. More complex interactions within the environment necessitate both identification and categorisation of objects within the scene. This requires recovery of

such perceptually organized visual input, but such representations must then also be matched to like-format representations stored in memory (Wolfe, 1996).

The dominant psychological, physiological and computational models advocate such a feature-based dichotomous search system and include, most notably from Psychology, Feature Integration Theory, Texton Theory and Guided Search. These are rivaled chiefly by Similarity Theory, which does not support the serial/parallel dichotomy. Such theories will now be explored.

2.10 Feature Integration Theory

Treisman was one of the first to document the area of preattentive processing. She recognized that the acceptance of the existence of some form of early image decomposition along different stimulus dimensions creates two difficulties for psychological research. One is to define those "preattentive features" that are the visual primitives or basic elements of vision. The second concerns how they are put together again into the correct combinations to form the coherent world that we perceive (Treisman & Gelade 1980; Treisman & Souther 1986; Treisman & Gormican 1988; Treisman, 1991). Treisman and others have delineated a finite number of such preattentive features experimentally, and Treisman has integrated those into a Feature Integration Theory to attempt to explain the visual processes underlying perception. The basic construct of Feature Integration Theory (FIT) is to claim that the parallel stage identifies the basic visual features that are present, and that the slower, serial stage then combines these features to produce complex representations of visual objects. This model proposes the existence of a low-level human vision system composed of a set of feature maps and a separate master map of locations.

FIT (Treisman & Gelade, 1980; Treisman & Schmidt, 1982) suggests that retinal images are analysed into separate features, each represented in a separate feature map. This retinotopic map is topographic; neighbouring detectors represent the activity at neighbouring image points, and this retinotopic map is coded in parallel to the feature maps. Each map registers only one of the image features coded in the retinotopic map. Individual occurrences of the feature sum spatially to create a "pooled" activity. A subject can access a particular map to check for activity, and perhaps to determine the amount of activity. The maps code feature presence but not location, spatial arrangement, or relationships to activity in other maps. Location is held in a separate "master map of locations" that has links in to the feature maps (see Figure 2.23).

Treisman suggested a manageable number of feature maps, including one for each of the opponent colour primaries - green, red, yellow and blue, as well as separate maps for orientation, shape, texture and other preattentive features. The framework above provides a general hypothesis to explain how preattentive processing occurs. If the target has a unique feature, one can simply access the given feature map to see if any activity is occurring. Feature maps are encoded in parallel, so feature detection is almost instantaneous.

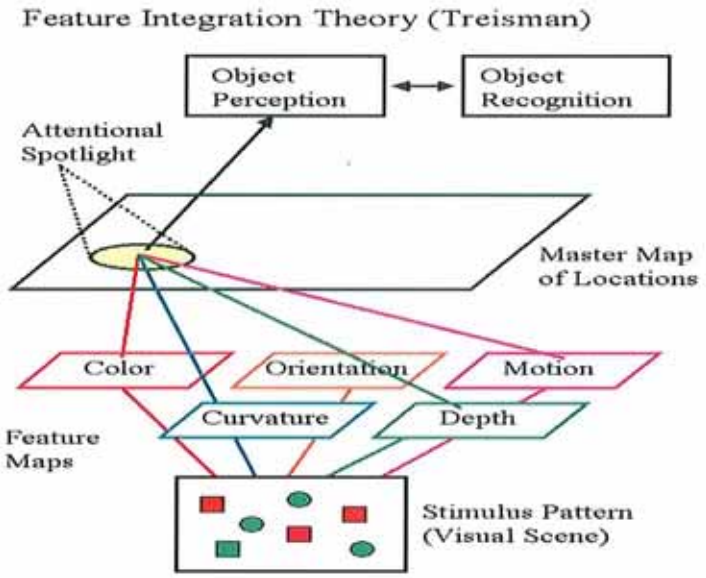


Figure 2.23: Treisman's feature integration model for early vision; individual spatiotopic feature maps represent dimensions such as colour, orientation etc. that can be accessed to detect feature activity; corresponding locations in each map are connected to a "master map of locations"; focused attention acts through a serial scan of the master map of locations. From: www.luc.edu/faculty/asutter/FIT.gif

FIT however predicts a different result when a target is composed of a conjunction of features and each distractor shares at least one of those features. In this case, the serial stage must process each element individually until it finds the target conjunction (Figure 2.24). A conjunction target cannot be detected by accessing an individual feature map. Activity there may be caused by the target, or by the distractors that share the given feature. The detection of a conjunction requires attention to integrate information across the feature maps. Each map must be serially inspected in order to detect the co-occurrence of the pre-specified features. In order to locate the target, one must search through the master map of locations, looking for an object with the correct

combination of features. This use of focused attention requires a relatively large amount of time and effort.

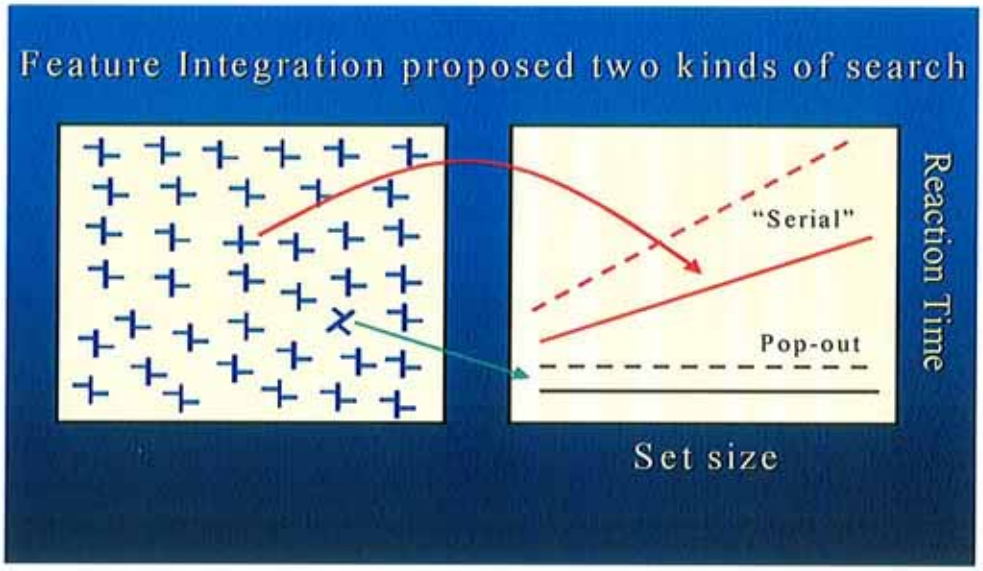


Figure 2.24: Parallel search for an orientation difference versus serial search for a target not defined by a basic feature difference (both target and distractor are composed of vertical and horizontal lines). Courtesy J. Wolfe.

In summary, the theory implies that search consists of three ordered processes: (i) detect: register pooled activity in feature maps; (ii) localize: use attention to link the activity to a location in the master map; and (iii) identify: perceive an object after all the features are glued together.

Detection can occur without localisation or identification because it does not require attention. Localisation, then, cannot occur until the observer applies attention to the master map. Lastly, after features are localized, they combine into identifiable objects.

Feature integration theory presents a strict dichotomy between the parallel and serial stages of visual search, represented by the difference between feature and conjunction searches for both pop-out and boundary detection tasks. Its ability to account for the

search process with relatively simple processes makes it very compelling. However data obtained since its inception provide certain difficulties for FIT, particularly in relation to the visual system's ability to perform conjunction searches. For instance, Egeth et al. (1984) showed evidence from conjunction searches suggesting that subjects were able to confine their search to elements of a single colour or a single shape, excluding a particular subset of the elements in parallel from the beginning, although they were still searching serially through the remaining elements.

More significantly, Nakayama & Silverman (1986) found that for conjunction search tasks for targets defined by size or stereoscopic depth, subjects completed the search in parallel. Subjects somehow isolated their search to a particular depth plane or to a particular scale, and can thus do a parallel search for the one unique element within that plane or scale (Figure 2.25). Conjunction tasks involving motion, colour and orientation have also been shown to be subject to full preattentive processing (Driver et al., 1992; Wolfe et al., 1989).

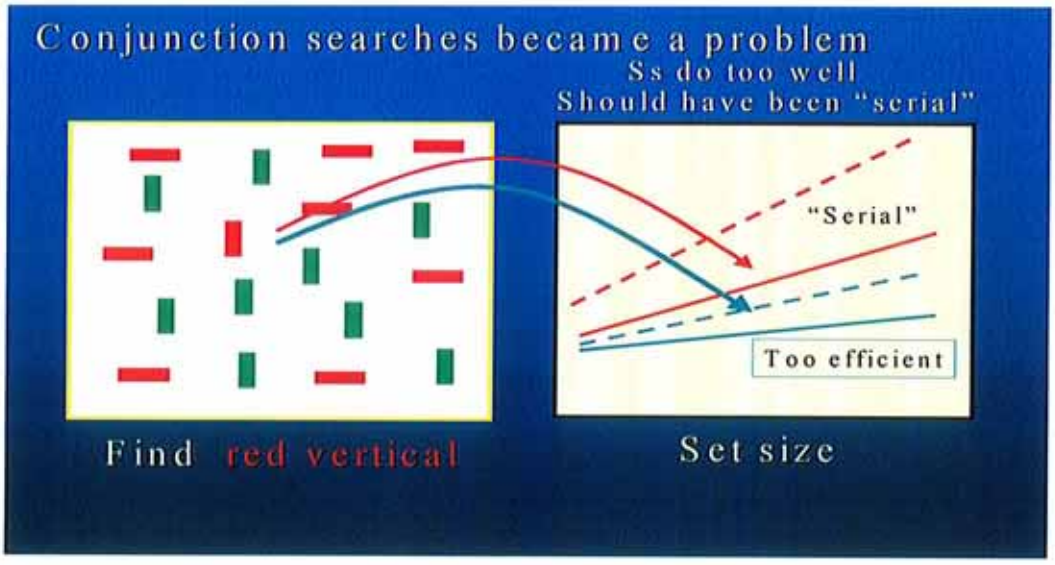


Figure 2.25: FIT cannot explain the efficient search for the red vertical line. Courtesy J. Wolfe.

FIT thus needed revision to account for such data. Treisman hypothesizes that a significant target – non-target feature difference would allow individual maps to ignore non-target information contained in the master map (Treisman & Gormican, 1988). It still does not account for such efficient conjunction search however. All red items above would be coded in the colour feature map. This map however would contain no information about orientation. The subject would therefore have to direct attention to the master map to find an item coded by both red and vertical orientation. This may be less serial however as all green items can be excluded from the search.

Treisman has since expanded her strict dichotomy of features being detected either in parallel or in serial (Treisman & Gormican, 1988; Treisman, 1991). She now presents parallel and serial as two ends of a spectrum. "More" and "less" are encoded on this spectrum, not just "present" and "absent". The amount of differentiation between the target and distractors for a given feature will affect search time (see section 2.12 Similarity Theory).

2.11 Texton Theory

Julesz was instrumental in expanding our understanding of the "where" and "what" we "see" in an image. His initial investigations focused on determination of whether variations in image properties such as contrast, orientation and curvature were seen by the low-level visual system. Based on these findings, he introduced his Texton Theory (TT) of how preattentive processing occurs.

The principal claims of Texton Theory are two-fold:

First, Texton Theory, like FIT, holds that the human visual system consists of two distinct systems: a preattentive system that operates instantaneously, in parallel, over a large visual field (at least 14^0 of arc) and an attentive system that operates by moving a small "spotlight" serially over the visual array in 50-msec steps to produce complex representations of visual objects. From this feature perspective, both TT and FIT are virtually identical (except that they employ different terminologies). Second, there are only a small number of textons and the preattentive system is limited to detecting local differences in the type and number of these textons in the visual field.

Texton Theory is a form of what has become known as a class of "Interrupt Theories" (Green, 1992). Several studies (Atkinson & Braddick, 1989; Johnston & Pashler, 1990; Sagi & Julesz, 1985a) claim that observers could not only detect but also localize targets in parallel. This is in direct conflict to the claims of FIT that such location information is not accessible except by serial examination of the master map. One interpretation of this finding (Sagi & Julesz, 1985; Nothdurft 1991) is that preattentive vision allows observers to initially detect and locate a "difference signal" where there is a break in a feature gradient. The discontinuity (interrupt) itself conveys no identity information so the source of the discontinuity cannot be identified until the observer moves focal attention to the location of the signal.

Johnston and Pashler (1990) offer a similar theory. They found that localisation could be better than identification and suggest that observers detect a featureless signal that cannot be identified without attention. They differ however, by saying that the signal is an interrupt from a particular feature rather than from a texture discontinuity. Texton theory was ultimately based on three axioms.

(1) As with Feature Integration, Texton Theory assumes that the visual system operates a "divide and conquer" strategy, utilizing the parallel preattentive system to rapidly perform a global analysis of the image features, which he labels "textons". A subsequent serial system then operates to focus attention on the image. Herein however lies the principal difference between Texton Theory and Feature Integration. Whereas Feature Integration assumes that all knowledge of feature location is lost during the preattentive stage of feature encoding, Texton Theory assumes that, not alone does the preattentive system detect the textons; it also knows where the texton gradients occur. As with Feature Integration the system is at this stage unaware of what the textons are.

(2) Textons can be classified into the following groups

- Non-overlapping line segments with specific length, orientation, width, velocity, binocular disparity and flicker rate.
- Terminators (ends of lines) of line segments
- Crossing of line segments
- Elongated blobs (e.g. line segments, rectangles, ellipses –shape unimportant) with specific properties for length, width and orientation

(3) Texton gradients are established when neighbouring textons lie within a critical distance. Only a difference in textons or in their density can be detected preattentively. The presence of a texton is detected more easily than its absence.

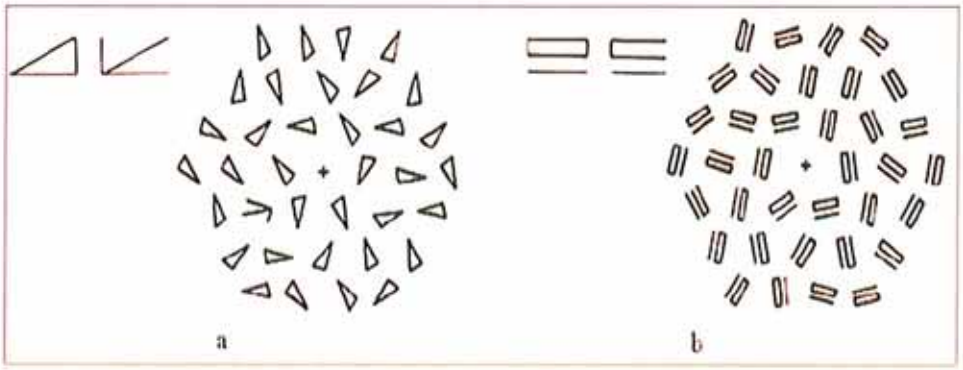


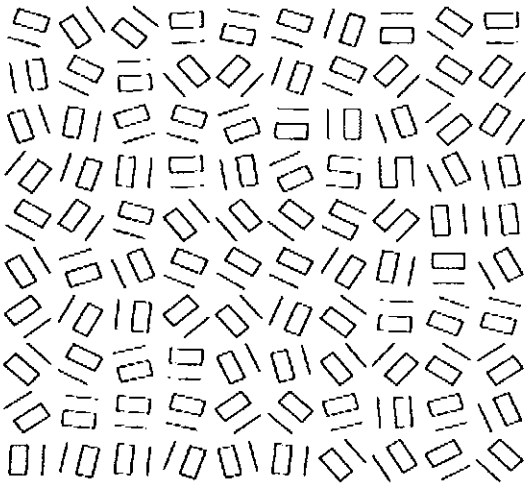
Figure 2.26: Two typical texton search paradigms. The search for the target in (a) takes place in parallel, while the search for the target in (b) is serial in nature (see Figure 2.27 below for explanation of the serial nature of task (b). From: Julesz (1981).

The claims of Texton Theory outlined above can be perceived intuitively by inspection of Figure 2.26 above. Figure 2.26a is composed of two elements: a triangular element and an arrow like element. Both elements contain one vertical line, one horizontal line and one diagonal line. They differ only in the location of the vertical line. The arrow target immediately pops out, being detected in parallel. Because the elements have the same lines, the pop-out cannot be as a result of the number or type of lines. One candidate visual property responsible for the segregation is line closure. This property categorizes the triangle but not the arrow. A second candidate is the number of line terminators. The triangle has no terminators, whereas the arrow has three. Julesz prefers the latter interpretation on the basis of Figure 2.26b.

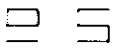
Figure 2.26b is also composed of two elements that differ in the location of a single line: an "S" – like element and an element resembling a supine "10". In addition to sharing three horizontal lines and two vertical lines, these elements each have two line terminators. Like Figure 2.26a, the two elements differ in that one has line closure and

the other has not. In contrast to Figure 2.26a, the region containing the "10s" is very difficult to distinguish. Thus Julesz argues that line closure cannot be detected preattentively when the number of line terminators is kept constant.

The stimuli used in Figure 2.26b are illustrated again in Figure 2.27 below in the form utilized by Julesz for boundary detection tasks. Again the textons do not segregate preattentively and the texture boundary is not easy to locate.



(c)



(a) (b)

Figure 2.27: An example of textons: two textons (a and b) that appear different in isolation, but have the same size, number of terminators, and join points; (c) a target group of b-textons is difficult to detect in a background of a-textons when a random rotation is applied. Such textons are indistinguishable based on texton equilibrium, having two line terminators each. From: Julesz (1981).

One potentially important aspect of texture segregation that is ignored by Texton Theory is the relative salience of the unique features. Texton theory predicts texture segregation on the basis of a simple difference in texton type or number. An alternative theory, expressed by Beck (1982), suggests that texture segregation may occur once

the variation in features between regions is greater than the variation in features within a region. Hence, texture segregation may not be determined by texton differences per se, but by the extent to which the unique textons in elements are salient in the context of the textons common to elements.

If Figure 2.26 is reconsidered from this perspective, an alternative explanation for the differential segregation of these two textures becomes apparent. Both textures are composed of elements that differ only in the location of a single vertical line. However, the unique line in Figure 2.26a is significantly longer than the unique line in Figure 2.26b; the texture difference is larger and therefore more salient. Relative differences in salience may therefore be sufficient to explain differences in texture segregation.

Enns (1986) tested the above hypotheses on whether textons are segregated on the basis of texton difference or by degree of saliency by altering the stimuli in Figure 2.26a + b to affect their saliency without altering their "texton" properties. This was achieved by simply shortening the length of the unique line in Figure 2.26a, and increasing the length of the unique line in Figure 2.26b. The new 2.26a target still had 3 line terminators compared to the triangle distractor with none, while both the target and distractor in the new version of Figure 2.26b had 2 terminators.

The results of Enns' experiments are not easily accommodated by texton theory. He found that the new target in Figure 2.26b was discriminated preattentively even though it contained no texton differences. In fact, these textures were more easily discriminated than the new Figure 2.26a target, which does contain texton differences.

These results support Beck's (1982) notion that texture regions are segregated through the computation of a similarity function that takes into account both common and unique features in a local area. Even more significantly, such context dependency of textons also raises questions about the strong dichotomy between preattentive and attentive vision (see section 2.12 Similarity Theory).

2.12 Similarity Theory

Like Feature Integration Theory, Similarity Theory deals with how search efficiency is determined by the nature of relevant (target) and irrelevant (non-target) stimuli in the visual scene. Whatever the visual task, limitations on our ability to "divide attention" require that we select relevant, and discard irrelevant information from the scene. Feature Integration argues that input from a visual display is processed in two successive stages, parallel feature mapping as the first stage of analysis, followed by the serial focused attention which is of limited capacity. Similarity theorists however present a new account, different from Feature Integration theory in several important respects.

First, the dichotomy between serial and parallel search has no real place in such a model, which is based on a continuum of search efficiency where search efficiency varies with the complexity of the task (Duncan & Humphreys, 1989- see Figure 2.28 below). Second, similarity theory is not based on a distinction between different stimulus attributes, but more abstractly on stimulus relations (similarities) that in theory can be specified for any attribute. Therefore, very similar stimulus principles control search difficulty whatever the search principles.

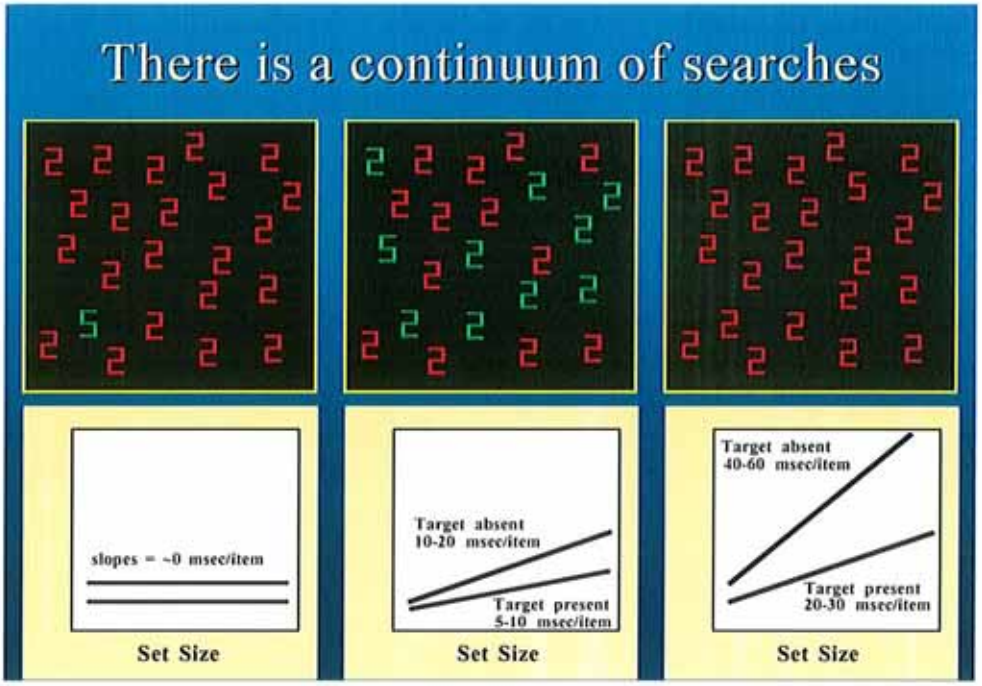


Figure 2.28: The task in each case is to locate the number "5". Set size (number of distractors) effects vary continuously, from none, when search is easy (left) to moderate (middle) and severe (right) as task difficulty varies. Courtesy J. Wolfe.

Quinlan & Humphreys (1987) investigated conjunction searches focusing on two factors. First, search time may depend on the number of items of information required to identify the target. Second, search time may depend on how easily a target can be distinguished from its distractors, regardless of the presence of preattentive features. They argued that their experimental data was not easily explained by Feature Integration Theory. Duncan & Humphreys (1989) proceeded to their own explanation of preattentive processing, namely - Similarity Theory.

The Duncan & Humphreys model assumes that search ability varies continuously, depending on both the type of task and the display conditions (Duncan & Humphreys, 1989; Duncan, 1989). Search time is based on two criteria: firstly, similarity between

targets (T) and non-targets (N) and secondly, the amount of similarity between the non-targets themselves. These two factors affect search time as follows:

- As T – N similarity **increases**, search efficiency decreases and search time increases
- As N – N similarity **decreases**, search efficiency decreases and search time increases
- T – N similarity and N – N similarity are related (Figure 2.26):
  - Decreasing N – N similarity has little effect if T – N similarity is low
  - Increasing T – N similarity has little effect if N – N similarity is high

(A) (B)

Figure 2.29: Example of N-N similarity affecting search efficiency for a target shaped like the letter L: (a) high N-N (nontarget-nontarget) similarity allows easy detection of target L; (b) low N-N similarity increases the difficulty of detecting the target L. From: Duncan & Humphreys (1989)

In Figures 2.29A + 2.29B above, both sets of distractors use the same features as the target - namely oriented, connected lines of a fixed length. Yet experimental results show that the search for the target L in display 2.29A produces a slope of ~4.5msec per additional distractor while displays like 2.29B produce slopes of 54.5msec per

additional distractor. The set-size effects seen in such cases of non-target heterogeneity are a large departure from unlimited capacity parallel search even though the target has a unique stroke (preattentive feature).

The results of this and other experiments show that in visual search, the effect of adding irrelevant (non-target) information to a display varies continuously; from little or none (or even a beneficial effect – Sagi & Julesz, 1987) to at least 100msec/item (Quinlan & Humphreys, 1987; Treisman & Gelade, 1980, Sagi & Julesz, 1987). Such continuations in search efficiency are consistent with a variety of theoretical positions but Duncan & Humphreys (1989) hold that this is based on continuous variables rather than the serial/parallel dichotomy.

Duncan & Humphreys proposed a three-step theory of visual selection to explain phenomena they felt were inconsistent with existing feature integration theory.

1: The visual field is segmented into structural units. Individual structural units share some common property (e.g. spatial proximity, hue, shape, motion). Each structural unit may again be segmented into smaller units. This produces a hierarchical representation of the visual field. Within the hierarchy, each structural unit is described by a set of properties (e.g. spatial location, hue, texture, size). This segmentation occurs in parallel.

2: Because access to visual short-term memory is limited, they assume that there exists a limited resource that is allocated among structural units. Because vision is being directed to search for particular information, a template of this information being sought is available. Each structural unit is compared to this template. The better the

match the more resources allocated to the given structural unit, relative to other units with a poorer match.

3: Because units are grouped in a hierarchy, a poor match between the template and a structural unit allows efficient rejection of other units that are strongly grouped to the rejected unit.

Structural units with a relatively large number of resources have the highest probability of access to visual short-term memory. Thus, structural units that most closely match the template of information being sought are presented to the visual short-term memory first. Search speed is a function of the speed of resource allocation and the amount of competition for access to the visual short-term memory.

Given these three steps, we can see how T – N and N – N similarities affect search efficiency. Increased T – N similarity means more structural units match the template, so competition for visual short-term memory access increases. Decreased N – N similarity means observers cannot efficiently reject large numbers of strongly grouped structural units, so resource allocation time and search time increases. Thus, Similarity Theory makes feature and conjunction search tasks very similar in principal. By manipulating T – N and N – N similarity, either task can be made very simple or very difficult.

The principal achievement of Similarity Theory is to give attention to interactions between elements in a display, rather than merely concentrating on the classification of each element as a target or non-target. Regardless of the precise mechanism of interactions – dichotomous or continuous, the basic principles are the same; some

information is coded very rapidly while other requires attention. Similarity builds on the foundations of Feature Integration rather than causing any significant destruction to its principles. Possibly the most complete and all encompassing theory of visual search however is that of Guided Search.

2.13 Guided Search Theory

Like Feature Integration, Guided Search distinguishes between a preattentive parallel stage that processes basic feature information into feature maps, and a limited-capacity serial stage for more complex operations such as face recognition and object identification. The spatial deployment of the limited-capacity process is under attentional control.

It is common knowledge (as outlined above) that we can pay attention (at any one time) to only a small amount of the information present in a visual scene. Experimentally, it is easy to confirm that people can take up and report only a small amount of the information contained in a visual display. Such a limitation imposes a strong requirement for selection. Ideally we should confine attention to that information needed to guide current behaviour, and again it is easy to confirm that people can use many different selection criteria (features) to choose which information to "see" in a briefly glimpsed scene.

The heart of the Guided Search model is the idea that attentional deployment of limited resources is guided by the output of the earlier parallel processes (Wolfe, 1994a). It is obvious that the visual system's limited resources should not be deployed and are not deployed in a random fashion. They are under attentional control. By "paying" attention to a specific locus in the visual field, we bring to bear at that locus some of

these limited- capacity visual processes. Information gathered by the parallel front end is used to restrict the deployment of the limited-capacity processes to those parts of the visual field most likely to contain items of interest. The guidance is not perfect but is far more efficient than random deployment of attention.

The control of this deployment can be exogenous, based on the properties of the visual stimuli, which will be most useful for survival mechanisms, or endogenous, based on the demands of the "user" of the visual system when searching for specific items in our increasingly cluttered environment (Posner, 1980). These are not mutually exclusive.

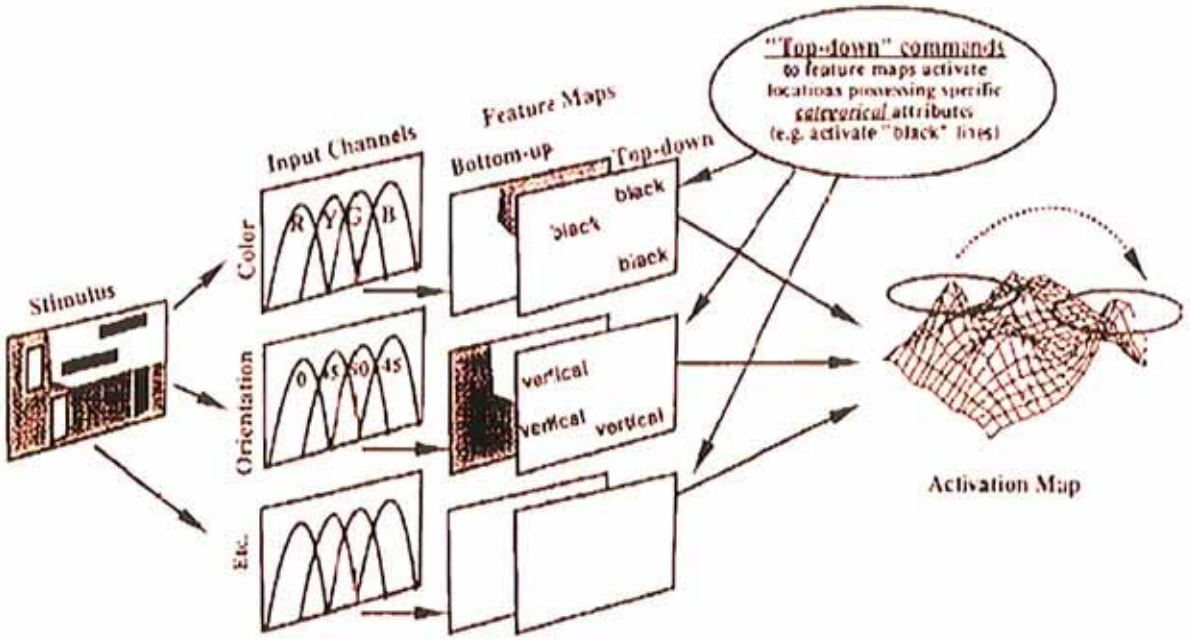


Figure 2.30: Framework for guided search, user wants to find a black vertical target; image is filtered through broadly-tuned "categorical" channels into categories for each feature map, bottom-up and top-down activation "mark" regions of the image; an activation map is built by combining bottom-up and top-down information, attention is draw to the highest "hills" in the map. From: Wolfe, 1994

Guided search holds that an activation map based on bottom-up and top-down information is constructed during visual search. Early vision divides an image into individual feature maps (Figure 2.30). There is one map for each feature type and within each map a feature is filtered into multiple categories. For example, in the colour map there might be independent representations for red, green, blue and yellow. Wolfe (1992) has also found evidence that orientation is categorised into steep, shallow, right and left.

The relationship between values within a feature map is different than the relationship between values from different maps (i.e. the relationship between "red" and "blue" is different to the relationship between "blue" and "shallow").

Bottom-up activation follows feature categorisation. It measures how different an element is from its neighbours. Differences for each feature map are computed and combined. Top-down activation is a user-driven attempt to find items with a specific property or set of properties. For example, visual search for a green target would generate a top-down request that activates "green" locations.

Figure 2.30 shows how Wolfe (1994) conceives of the activation map as receiving a combination of bottom-up and top-down activation. The weights assigned to these two values are task dependent. A conjunction search would place priority on top-down information, as bottom-up results are, in essence, useless. Search for a target with a unique feature would assign a high weight to bottom-up activation. Hills in the activation map mark regions that generated a relatively large amount of top-down or bottom-up influence. There is no information in the activation map about the source of the hill. High activation from a colour map looks exactly the same as that from an orientation map. A subject's attention is drawn from hill to hill in order of decreasing activation.

Guided search thus explains the dissociation of certain "efficient" conjunction search experimental results from the basic predictions of earlier theories (see Figures 2.31 + 2.32 + 2.33). Such experimental results were previously problematic for traditional two-stage search theories.

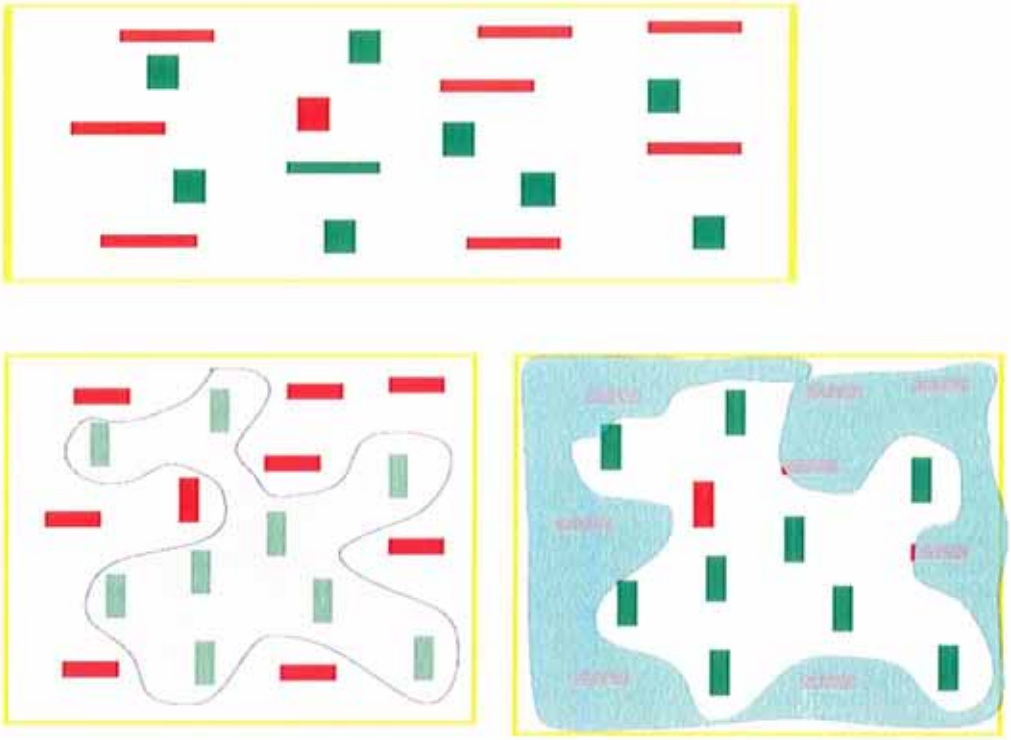


Figure 2.31: Preattentive mechanisms process all red items (A) in parallel to a colour feature map. All vertical elements (B) are also processed in parallel to an orientation map. Courtesy J. Wolfe.

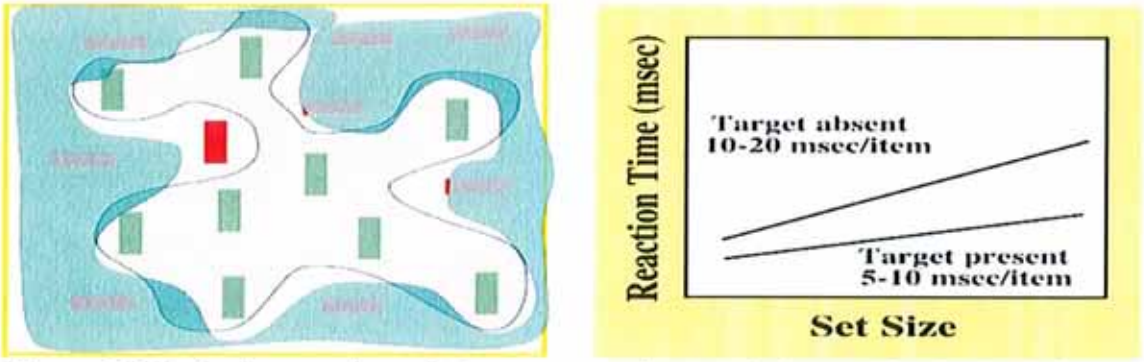


Figure 2.32: The intersection of these two sets is a good place to deploy attention. Because both conjunctions were coded in parallel, preattentive processes guide the deployment of attention and search is highly efficient. Courtesy J. Wolfe.

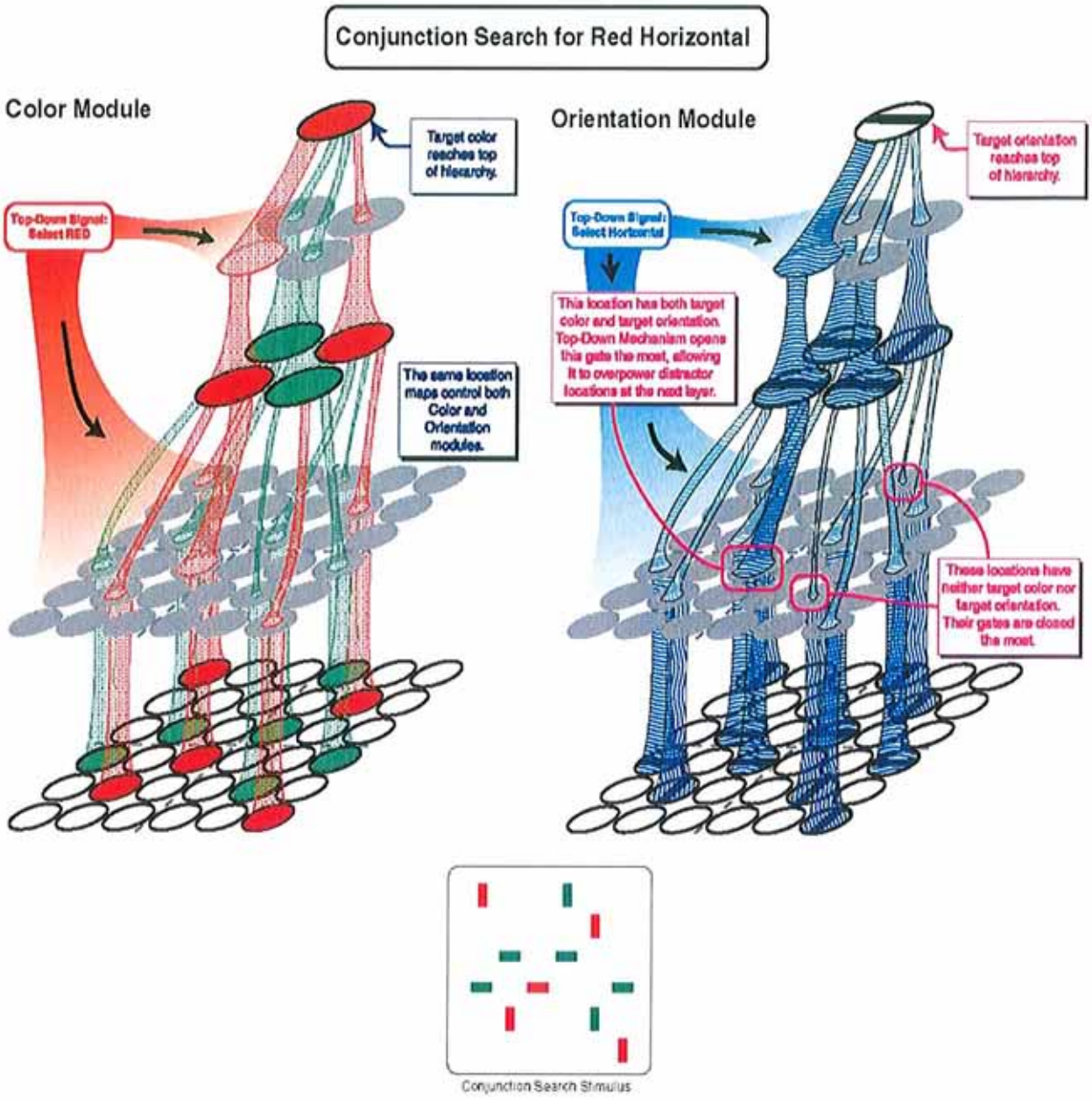


Figure 2.33: Independent parallel processing facilitates the rapid attentional deployment to areas of the visual field containing the target (defined by its horizontal orientation and its red colour). Top-down attentional requirements dictate bottom-up processing strategies. From: http://people.umass.edu/.../ ConjSearch.CN96.JPEG.

The architecture of feature processes feeding an activation map makes it possible to guide attention to likely loci for targets defined by conjunctions of two or more features, even though no parallel process, by itself, is sensitive to conjunctive properties. In a noise free system, conjunction searches would be no more difficult than the search for salient single

features. Search for conjunctions can be highly efficient with slopes near 0ms/item (e.g. Wolfe, 1992a), but, in general, conjunction searches are somewhat less efficient than feature searches with slopes in the vicinity of 5-12msec/item.

In Guided Search, parallel, serial and guided searches are not qualitatively different. Wolfe takes account of the similarity effects noted by Duncan & Humphrey's (1989), and suggests that the above searches lie on a continuum defined by the signal-to-noise ratio in the activation map.

Thus, parallel search occurs when the activation signal is so much larger than the background noise that attention is deployed first to the target location on all target present trials. It is therefore independent of set size.

A serial search occurs in the absence of parallel guidance when preattentive processes cannot differentiate between targets and distractors. Search therefore is in a random fashion throughout the entire set and is therefore affected by set size.

In a guided search, the activation signal from the preattentive process biases deployment of attention toward the target item but some distractor locations develop comparable levels of activation. The result is a serial search through a smaller subset of items and is therefore more efficient.

2.13.1 Deployment of Attention

Guided search treats the deployment of attention as a serial step in processing. Attention is either at one location or another. If it is at location x, it can only be redeployed to y with the passage of time. Feature modules can be thought of as a pair of topographic maps with hills of higher activation marking locations receiving substantial bottom-up or top-down activation (Figure 2.30). Attention is attracted to

the hills. The overall effect of activation in all maps is seen by summing the activations to create an activation map (similar to Treisman's Master map of Locations – Figure 2.34).

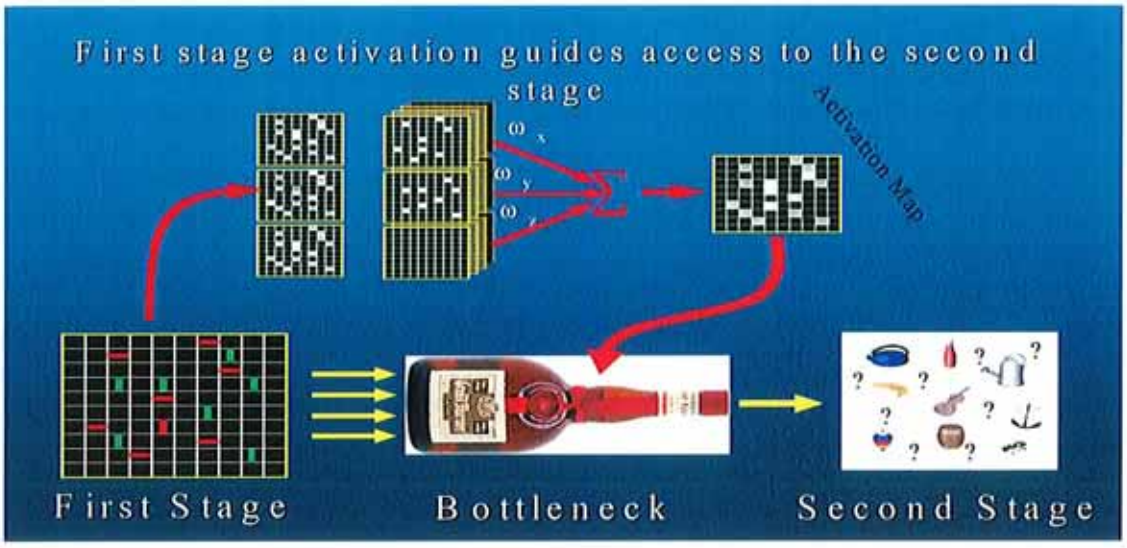


Figure 2.34: Local salience of the visual display is computed. It is local differences that create bottom-up salience. A limited set of coarse, categorical features is computed. A weighted sum of bottom-up and top-down activity creates an activation map. Courtesy J. Wolfe.

The activation map: All else being equal, local salience will be weighted heavily and will attract attention (bottom-up). Top-down instruction modifies the attentional requirements. The activation map guides re-entrant attentional selection of objects allowing rapid target detection.

The purpose of the activation map is to direct attention. In the absence of any endogenous commands to the contrary, attention will be placed at the locus of highest activation. The processes under attentional control then make the decision about the actual identity of the item. If the target is not found at that locus, attention will be redeployed to the locus with the next highest activation. There are however only a

limited number of factors that can serve to guide attention and the guidance of attention by such factors remains both coarse and categorical (Figure 2.35).

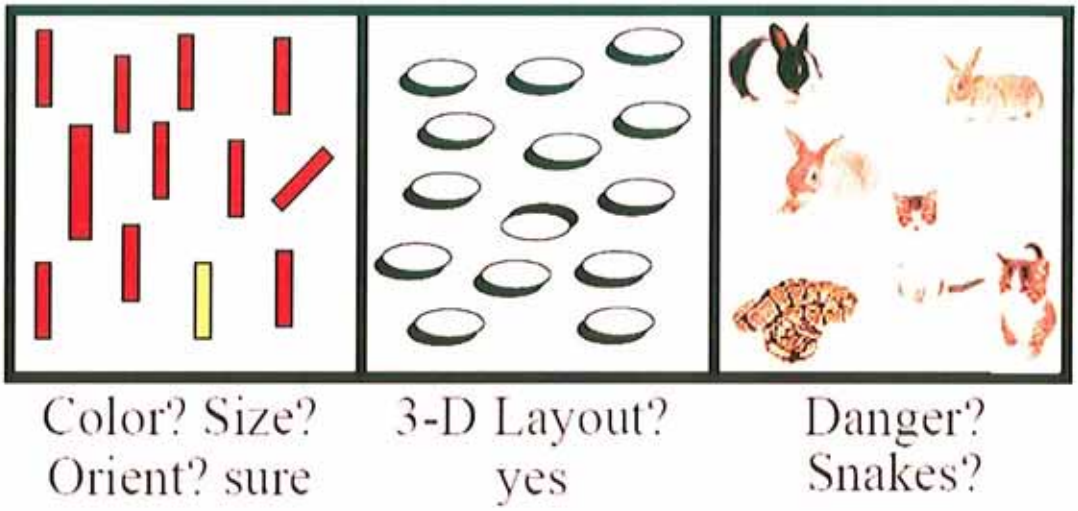
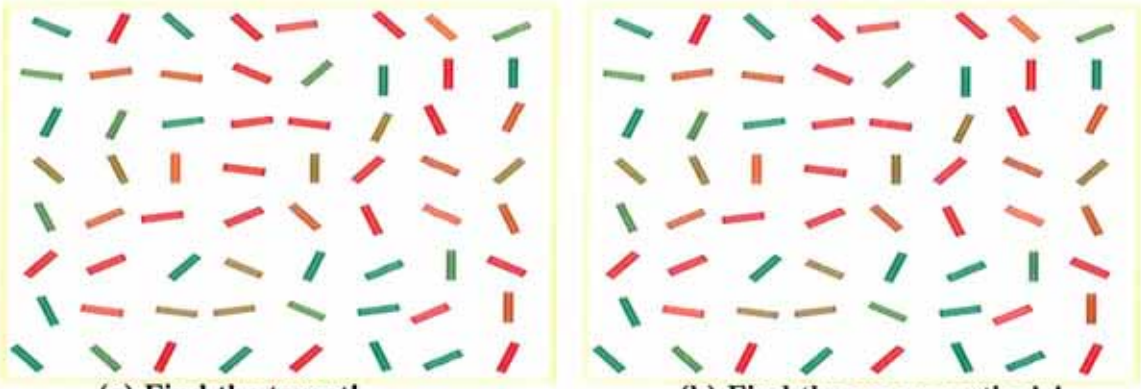


Figure 2.35: Some of the features (factors) that can serve to guide attention such as all basic stimulus features (colour, orientation etc) and including detection of threatening items. Other features like novelty and the presence of intersections appear not to be capable of guidance. Courtesy J. Wolfe.

The activation map cannot be a simple sum of independent activations. It must be weighted to emphasize useful information and limit the impact of useless activation. For example, all the targets in Figure 2.36 will generate substantial bottom-up activity for all colours and orientations.

If the target is a green vertical line, then efficient search requires that all other colour activations, and all other orientation activations do not mask the activations of the relevant targets. Thus the weighting in this case would be highest for green and for vertical. The intersection of these activations indicates the target location.



(a) Find the target! (b) Find the green verticals!

Figure 2.36: (a) Bottom-up salience is not enough (Hence, the use of the term "activation" not "salience" map). (b)Top-down guidance gives weight to what you want and access to the activation map allows target detection. Courtesy J. Wolfe

2.13.2 Guided Search in the Real World

Guided search theory is very much a work in progress currently incorporating four revised versions. Guided Search 3.0 (Wolfe, 1994b; Wolfe & Gancarz, 1996) expands GS2 by outlining a model of visual search that can handle real world images (Figures 2.37 + 2.38). Two important factors delineate real-world search from that performed with basic lab stimuli.

First, the eyes move during real world visual search. Most searches involve interplay of covert attentional movements and overt eye movements. Second, account must be taken of the fact that visual processing is much more detailed at the fovea. Presumably, eye movements in search exist to direct the fovea toward regions of interest. It has been shown that viewers spend more time analysing the centre of an image (Enoch, 1959a & b) and that eccentricity has an adverse effect on search performance (Carrasco et al., 1995), with targets closer to fixation located more accurately and more quickly.

Figure 2.37: The architecture of Guided Search 3.0. Wolfe & Gancarz (1996)

In Guided Search, attention serves as a gate, allowing feature information from only one object at a time to reach higher processes such as object recognition. This attentional gate is under the control of the activation map. Activity in the activation map is a weighted sum of activity in the preattentive feature maps. The activation map allows featural information about new items to pass through to the identification stage. If the selected item is not the target, feedback from the identification stage to the activation map inhibits that item. To identify the next item, the eyes need to move.

In order to move the eyes a saccade map (the GS3 analogue of the superior colliculus) is created (Sheinberg & Zelinsky, 1993). Every 200-250 milliseconds, the eyes are moved to the point of highest activation in the saccade map. The Guided Search architecture incorporates a cooperative relationship between eye movements and attentional deployments. Because central portions of the visual field are overrepresented in the feature maps, activation tends to be highest for central items.

Thus, during a fixation, attention is deployed to four or five central items. Assuming these are not targets, their representations are inhibited in the activation map. As a result, when it is time for the eyes to move, they foveate new items. These are then examined by attention and this process repeats until the target is found.

Figure 2.38: Typical GS3 scan paths for face recognition. Selective attention is deployed to a small number of facial locations. Note that face recognition employs increasing complexities of higher cortical analysis but does illustrate the scan paths generated through selective attention. (Yamada & Cottrell, 1995).

The achievements of Guided Search are four-fold.

First, it easily explains traditional parallel search. Target elements produce significantly higher levels of activation than distractors, resulting in pop-out regardless of the number of distractors.

Second, it accounts for the Duncan & Humphreys similarity theory results (see Figure 2.29). Low N-N similarity causes distractors to report higher bottom-up activation since they now differ from their neighbours. High T – N similarity causes a reduction in the target elements' bottom-up activation.

Third, and more importantly, it also provides a valid explanation for efficient conjunction search facilitated by user-driven activation. In Feature Integration, parallel capabilities are underexploited. Guided Search models a parallel guidance system to combine feature dimensions without the need to build computationally expensive conjunction representations at each location. This model puts the feature detection apparatus to better use and accounts for data at odds with Feature Integration.

Finally, it also accounts for the speed of visual processing of everyday tasks. Feature Integration cannot account for the almost immediate identification of everyday objects in more complex scenes. Guided Search facilitates rapid visual processing once items do not have similar size, shape properties, direction and velocity of movement. The search strategy it now appears, consists of two broadly parallel stages, an initial feature detection system, and a final object recognition system, both linked by a limited-capacity serial stage (see Figure 2.39).

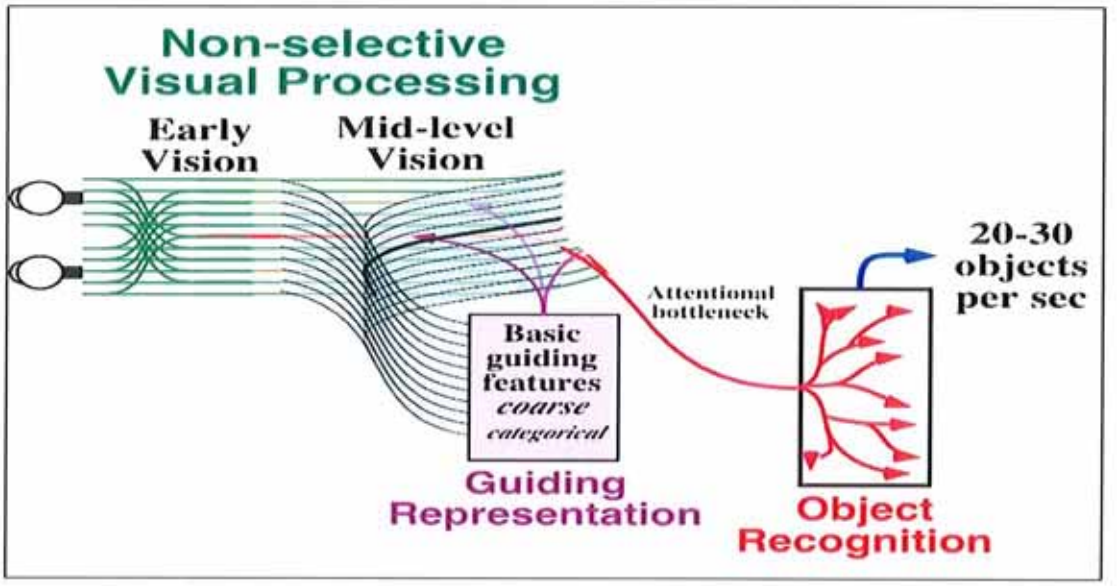


Figure 2.39: Basic features coded in parallel and used to guide attentional deployment through the serial bottleneck. Object recognition is broadly parallel once guidance mechanisms are employed. Courtesy J. Wolfe.

2.14 Conclusions

To summarise, physiological, computational and psychological research all lead to the notion that early vision represents images in feature modules. All concur, that early mechanisms, whether termed preattentive, parallel or efficient, whether dichotomous or continuous, serve to process basic features rapidly and accurately. Relevant or unique feature components thus pop-out and/or segment from the background noise.

Recent data from Nothdurft (2002) and Turatto & Galfano (2001) show that visual search for a target is aided by drawing attention to it (by colour or movement or whatever). So maybe pop-out happens when attention is involuntarily drawn to a local discontinuity which happens to be the target.

It is clear that there are many factors (both low-level and high-level) that will determine whether the target captures attention. When this does not happen you need to search for the target, which is a separate process requiring the integration of eye movements and attentional resources.

The efficiency of search is also affected by lots of separate factors. It is no longer enough to say that efficient search is the mark of a basic feature because there are situations in which search is very efficient even though no single feature defines the target (e.g. Theeuwes & Kooi, 1994).

The theoretical rationales outlined above may be different, but the message is clear: the visual system operates with a divide-and-conquer strategy. Questions remain, such as "What is the system architecture?" and "What puts Humpty Dumpty together again?" The answers to such questions requires deeper exploration of multiple facets of visual perception such as post-attentive vision, change blindness, eye movements, cortical organisation, visual short-term memory and many more which are beyond the scope of this investigation

For our purposes however, what is important is that known preattentive stimuli will be distinguished rapidly and accurately from a distracting background by the healthy visual system.

Whether (and to what extent) conditions affecting the integrity of the low-level visual system (including retinal architecture, visual pathway and low-level cortical areas)

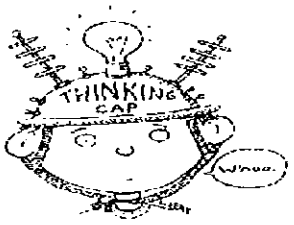
degrade the parallel capabilities of the visual system remains to be seen. Given the exhaustive research available on such stimuli, it will not prove difficult to design experimental stimuli suitable for such an investigation across a range of disease processes.

CHAPTER 3

VISUAL PERCEPTION

3.1 Introduction

Understanding visual perception requires integration of a diverse body of knowledge including physics and optics, neuroanatomy and neurophysiology, psychology and computation. It is not possible to explain our perplexing ability to perceive the three-dimensional layout of the environment by simply analysing the properties of light and the workings of the ocular refractive system to place a flat (curved) two-dimensional image (consisting of fleeting patterns of flickering light) on the retina of each eye. It is also not possible to understand why retinal ganglion cells and lateral geniculate neurons have the receptive fields they do simply by studying their anatomy and physiology in isolation. Trying to understand perception by studying neurons alone is like trying to understand how birds fly by studying their feathers alone.



TO SEE IS...TO THINK (Salvador Dalí).

Perception is not just to reflect the world in a simple manner. Perceived size is not the same as physical size, perceived brightness is not the same as physical intensity (Purves et al., 2004), perceived velocity is not physical velocity and so on for many other perceptual attributes. Moreover, the perception of composite stimuli often elicits interpretations that are not present when the components are perceived separately. Or to put it in other words: The whole is different from the sum of its parts. The nature of perception is rather to provide a useful description of objects in the outside world, instead of being an accurate mirror image of the physical world. This description has to represent features that are relevant to our behavior.

Hermann von Helmholtz, one of the founding fathers of the scientific study of visual perception, held vision to be a form of unconscious inference: vision is a matter of

deriving a probable interpretation for incomplete data. The general goal is to identify, as accurately as possible, the features of our environment: roughly, what objects are present where.

Our ability to perceive the 3D structure of the world around us is critical for (1) recognising objects, (2) working out where we are and where we want to navigate to and (3) for moving our bodies to interact with interesting objects and avoid dangerous objects. Although it may seem like an easy skill, working out the 3D structure of the environment involves a great deal of neural processing, and we do not yet have a full understanding of how the brain achieves it. Indeed, any attempt to explain the complexities of human visual perception must concede that the study of the biological basis of sensation and perception is a burgeoning field and technical advances are eliciting new findings that challenge our conceptions of how vision and the brain operate.

Figure 3.1: Cartoon illustrating the strange and wonderful business of perception. From: Spratt (2002)

The human visual system can detect and discriminate between an incredibly diverse assortment of stimuli that may be chromatic or achromatic, in motion or not, patterned or unpatterned, two-dimensional or three. Remarkably, the neural end product of visual stimuli impacting upon the retina is, in one sense, always the same. After the complexities of phototransduction, lateral interactions provided by horizontal and amacrine cells, and integration of signals by ganglion cell dendrites only the constantly changing stream of action potentials propagating along ganglion cell axons is left to inform our visual perception. These seemingly similar signals must somehow be processed in the subcortex and cortex to create the full range of visual percepts we experience. To further understand visual perception requires analysis of the anatomical and physiological neural interactions along the visual pathway, identification of the discrete anatomical pathways that carry the signal and clarification of what information the signals actually carry.

3.2 Historical Perspective

The relationship between vision and the eye must have been understood from the earliest times of human existence. The Greeks of 600-400 B.C. are believed to be the first to systematically study the anatomical organisation of the visual system (Polyak, 1957). The most prolific of medical scientists however was Galen (129-201 A.D.). Following Galen, very little advancement in understanding of the basic anatomy and function of the central visual system occurred over the next thousand years. Galen's teaching continued to be echoed in the beliefs of the humanist scientists such as Da Vinci (who pictorially described the same optic fibre to lateral ventricle pathway- Figure 3.2) and Des Cartes (who promoted the view of nerves carrying animal spirits).

Figure 3.2: Left: Diagrammatic representation of the Arab interpretation of Galen's visual system, from the oldest existing copy of the Book of Optics by Ibn Al-Haitham, an Arab physicist written in the 11 century A.D. Polyak (1957) Right: Drawing by Leonardo da Vinci of the projection of the eyes to the ventricles of the brain. From: Polyak (1957).

Between 1600 and 1860 A.D. significant advances were made, with anatomical investigations describing the structure of the visual pathway and revealing the six cortical layers. The notion of retinotopic organization also began to gain wide acceptance.

More recent advances in histological preparation (nerve fibre staining protocols of Wigert and Nissl, and the Golgi technique for labeling individual cells), the development of electrical recording techniques using microelectrodes to study single cells/fibres in the retina and optic tract (Hartline, 1938; Kuffler, 1953), in the somatosensory cortex (Mountcastle, 1957; Powell & Mountcastle, 1959), and in the visual cortex (Hubel & Wiesel, 1959; 1962;1968; 1974) in particular led to a boom in cellular studies of the visual cortex. More recent advances such as the development of electron microscopy and the development of "tracer" dyes have allowed researchers to describe the detail of synaptic connections and delineate the feed-forward and feedback pathways in the visual system.

The more recent development of positron emission tomography and functional magnetic resonance imaging techniques has further enhanced the ability to link structure with function in the brain (e.g. Menon, 2001).

3.3 Anatomy of the Visual Pathway

The visual pathway consists of a series of cells and synapses that carry visual information from the environment to the brain for perception. It includes the retina, optic nerve, optic chiasm, optic tract, lateral geniculate nucleus, optic radiations and visual cortex. The peculiarities of the pathway provide important clues to the clinician when diagnosing diseases of the eye.

3.3.1 Retina and Optic Nerve

Retinal capture of light photons occurs at the photoreceptor level of the retina. Such light capture ultimately leads to electrical signal generation that travels through the retinal layers to the ganglion cell layer. The ganglion cell axons course takes them through the intraocular region, which comprises the optic nerve head, at which the nerve fibres make a 90 degree turn and exit as the optic nerve. The microstructure in this intraocular region is complex (see section 4.7) but it is sufficient to say that the retinal ganglion cell axons, which are usually unmyelinated at this point, are divided into small bundles or fascicles (approximately 1000 such fascicles in each nerve) as they pass through the astrocytic and collagenous columns that comprise the lamina cribrosa in this region. This fascicular organisation is maintained along much of the rest of the nerve's course (Warwick, 1976).

Behind the lamina cribrosa, within the intraorbital segment, the diameter of the optic nerve increases by about 100% (Warwick, 1976). This increase is the outcome of two,

related structural changes of the retinal ganglion cells at this level. There is an increase in the diameter of the majority of the individual ganglion cell axons, and each axon gains a myelin sheath important for the propagation of nerve impulses along its length. The optic nerve necessarily takes a circuitous route to the apex of the orbit so that it is approximately 5 – 8mm longer than necessary to facilitate free nerve rotation during eye movement (Unsold & Hoyt, 1980). The intracanalicular portion takes the nerve through the optic canal in the sphenoid bone where it begins the intracranial segment ascending from the cranial opening of the canal where it fuses with the optic nerve of the fellow eye to form the optic chiasm.

3.3.2 Optic Chiasm

The optic chiasm lies at the base of the anterior hypothalamus, below the floor of the third ventricle, within the circle of Willis. Approximately 1cm below the chiasm lies the pituitary gland. The chiasm is the site of partial decussation of retinal ganglion cell axons. Those axons that originate in the nasal halves of each retina cross the midline from each optic nerve and pass to the optic tract of the opposite hemisphere; those from the temporal halves remain uncrossed and course into the optic tract of the ipsilateral hemisphere.

3.3.3 Optic Tract

The optic tract is a cylindrical, slightly flattened band of fibres that runs from the posterolateral corner of the optic chiasm to the LGNd (Parravano et al., 1993). Most of the fibres (which are still the retinal ganglion cell axons) terminate in the LGNd. Fibres from the retinal ganglion cells may branch so that the same cell sends fibres to various target structures or some axons may be destined for a specific structure. The afferent fibres of the pupillomotor reflex leave the optic tract before the LGNd and

pass to the pretectal nucleus in the midbrain (Figure 3.4). Other fibres project to several areas within the hypothalamus involved with the circadian rhythm and others terminate in the superior colliculus.

3.3.4 Dorsal Lateral Geniculate Nucleus (LGNd)

Information from all sensory systems, except the olfactory, pass through the thalamus before being transferred to the cerebral cortex. It is primarily through this nucleus that visual information involved in our conscious visual experience is processed and relayed to the visual cortex (Horton, 1992).

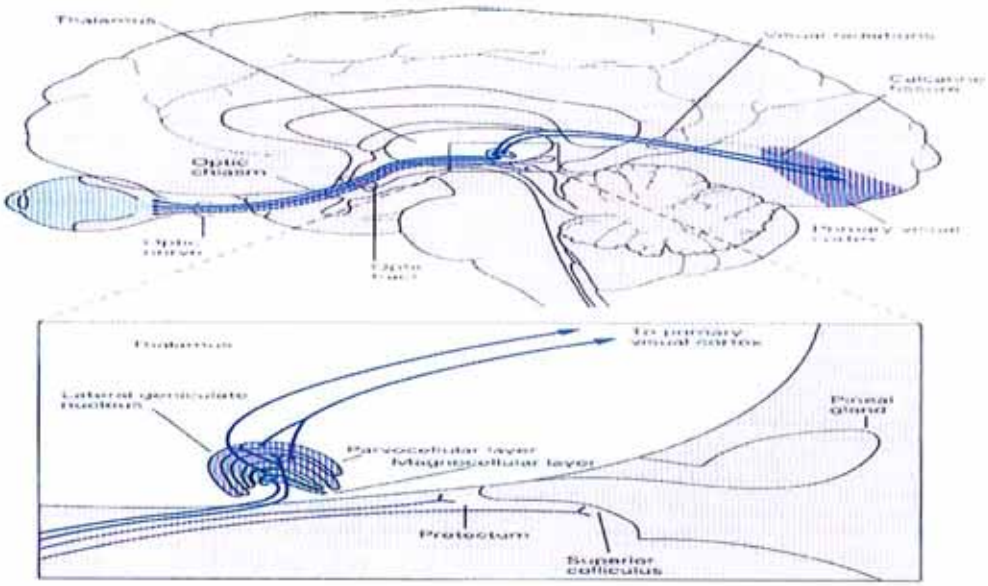


Figure 3.4: Information relay from the LGNd to the cortex. From: www.auto.ucl.ac.be/.../ LGN_files/image002.gif

The LGNd is a layered structure composed of six separate layers (see Figure 3.5) separated by six additional smaller layers. The cells within a layer are of the same type and three types have been identified according to size. Magnocellular layers contain large cells (Parasol or M cells), parvocellular layers contain medium to small cells (Midget or P cells) and koniocellular layers contain small cells. In coronal section these layers are visible one of top of the next.

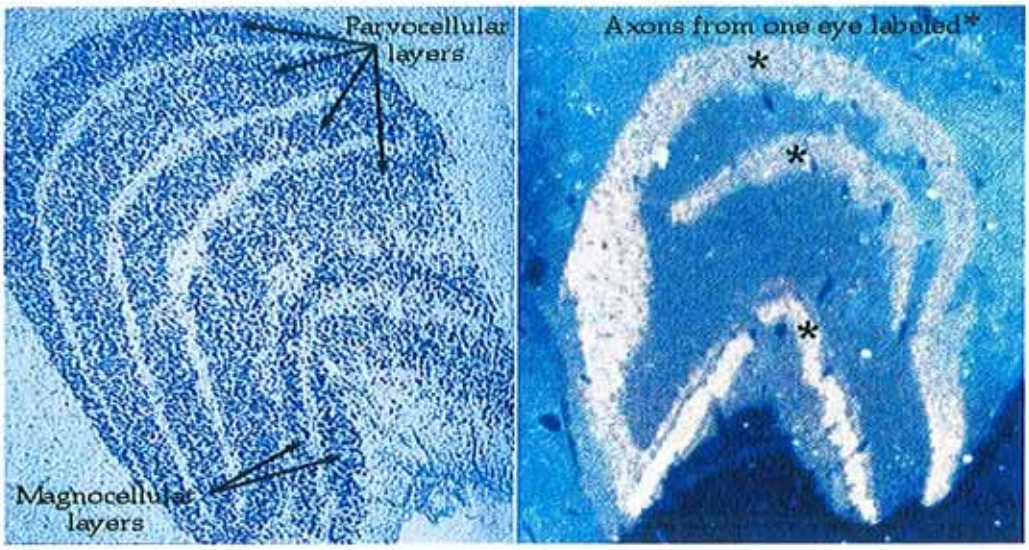


Figure 3.5: Coronal section of the LGNd. The two most ventral layers are magnocellular while the 4 most dorsal layers are parvocellular. The six koniocellular layers lie between each of the six main layers (these koniocellular layers contain relatively few cells). * Note the staining of layers 1, 4 and 6 from the contralateral nasal retina. From: www.cuyamaca.net/.../ images/image001.gif

The axons leave the LGNd as optic radiations.

3.3.5 Optic Radiations

The optic radiations spread out as they leave the LGNd, deep in the white matter of the cerebral hemispheres, sweeping laterally and inferiorly around the anterior tip of the temporal horn of the lateral ventricle (Figure 3.6). Some fibres loop into the temporal lobe before passing back to the parietal lobe en route to the occipital lobe. Within the parietal lobe the fibres pass lateral to the occipital horn of the lateral ventricle before terminating in the primary visual (striate) cortex (Krolak-Salmon et al., 2000).

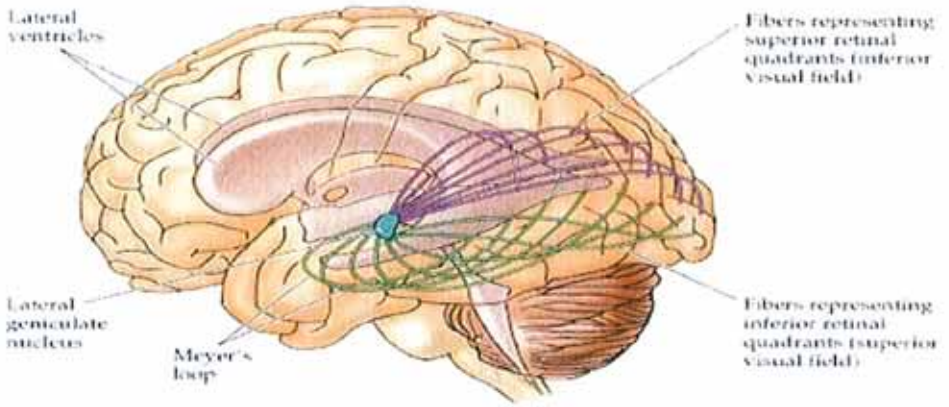


Figure 3.6: Optic radiations extending from the LGNd to the striate cortex.

From: www.city.ac.uk/.../vispath1lab/optcrads.JPG

3.3.6 Primary Visual (Striate) Cortex

The primary visual cortex (Brodmann area 17 or, according to most recent nomenclature, V1) is located almost entirely on the medial surface of the occipital lobe (just a small portion extends around the posterior pole onto the lateral surface), within the calcarine sulcus (see Figure 3.17). V1, while the primary receiving area for afferent information, is now recognised as one of a number of separate visual areas.

The first stop for visual information in the cortex is the striate cortex (V1) in the occipital lobe. All parts of the cortex are composed of six layers (see Figure 3.8 below) and each of these layers is involved in the same type of function regardless of where that layer is on the cortex. For example, the fourth layer from the surface of the brain, Layer 4, always receives input from sensory systems (Kolb and Whishaw, 1996). In the sensory areas of the brain, such as the visual cortex, this layer is very thick. This layer stains very darkly, which gives this first part of the visual cortex its name of striate cortex (Figure 3.7).

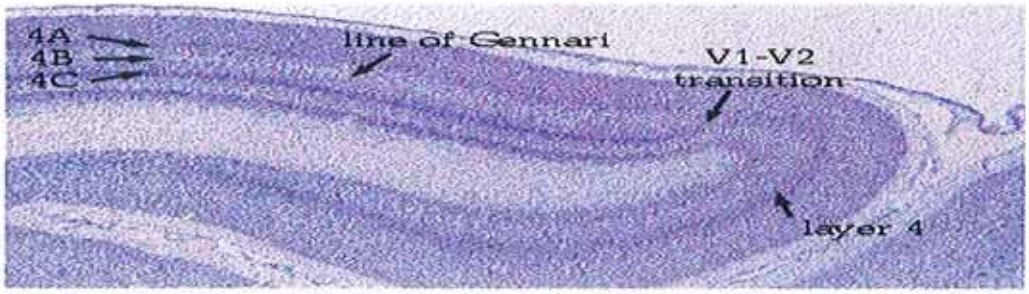


Figure 3.7: An illustration of the layers of the cortex as might be seen in V1. Layer 4 is where the input from the LGNd occurs and is the thickest layer here. It stains darkly giving this region one of its names, the striate cortex. From: http://thalamus.wustl.edu/course/cenvis.html

The anatomy of the primate primary visual cortex has been studied in great detail. The three basic organising principles of primate V1 are the (1) laminar and (2) columnar arrangement (Hubel & Wiesel, 1972) of excitatory and inhibitory neurons and (3) the regular spacing of anatomical/functional compartments revealed by cytochrome oxidase (CO) labelling.

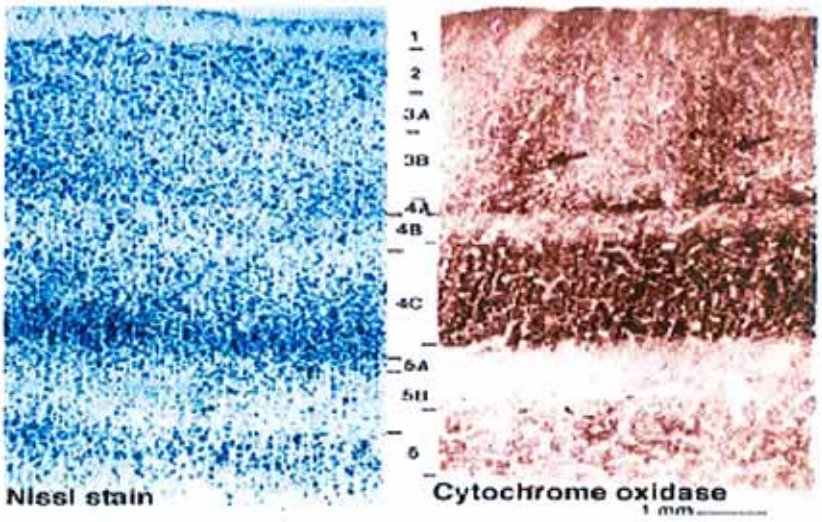


Figure 3.8: Nissl (left) and cytochrome oxidase (CO)(right) labeled cross sections of the visual cortex (V1) of the macaque monkey, showing individual layers labelled 1-6. From: www.retina.umh.es/.../gifswv/ VisualCortex-Nissl.gif

The 6 cortical layers of V1 introduced by Brodmann (see Figure 3.8 above - layer 1 most dorsal, layer 6 most ventral) have been subdivided time and again as additional aspects of the neurons and their connections have been revealed. Layer 4 (the "granular" layer), which receives the sensory input of the LGNd is divided into 4 horizontal sublayers: 4A, 4B, 4Cα, and 4Cβ. Layers 4Cα and 4Cβ are the major recipients of LGNd innervation. The LGNd magnocellular (M) and parvocellular (P) layers project to 4Cα and 4Cβ, (Figure 3.9) respectively (Hubel & Wiesel, 1972; Horton et al., 1990; Sawatari & Callaway, 1996). Thus, the M and P streams remain segregated at this stage.

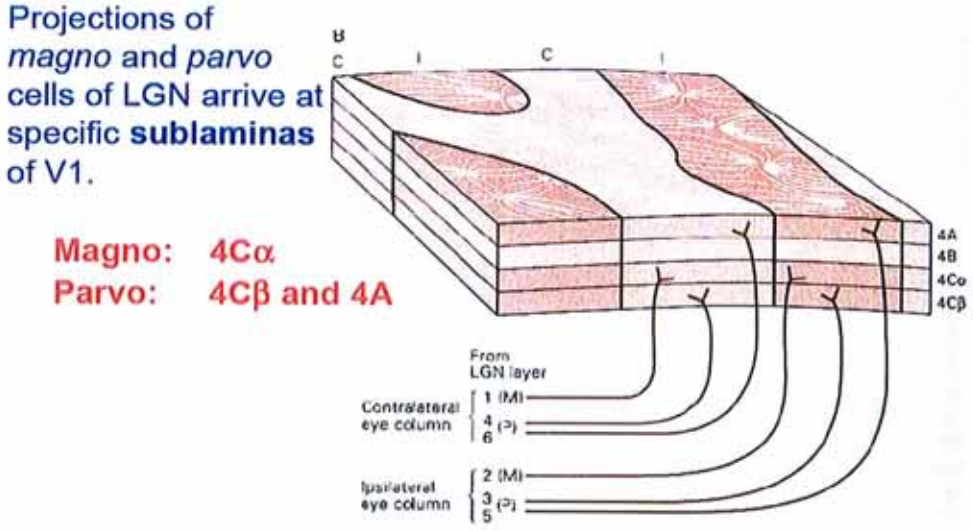


Figure 3.9: Projections from LGNd to V1 for the ipsilateral and contralateral eyes. Magno and Parvo pathways remain segregated.

From: http://www.cns.bu.edu/~ennio/ftp/530-f-2005-w03.pdf

Labeling of V1 and V2 for cytochrome oxidase (CO) content has revealed CO rich and poor regions termed "blobs" (or puff, spots, or patches) and "interblobs" in V1 and the thick, thin and pale stripes in V2.

In the primate, 5 principal visual areas have been identified, namely V1, V2, V3, V4 and V5. Each section is anatomically distinct and is thought to perform different functions relevant to our perception of the world. The current evidence suggests that V3 is involved with the processing of form, V4 with color constancy, and V5 complex motion processing. Some of these findings have been supported by the study of lesions in the occipital cortex. For example, a person with a lesion of the human region analogous to primate V4 on the left side of the brain would report having no colour vision in the right half of their visual world (Zeki, 1993).

Within the striate cortex (V1) the parvo and magno pathways are now segregated into three separate units that function independently: blobs, interblobs, and Layer 4b (Wong-Riley, 1979). Blobs receive inputs from both the magno and parvo system and seem to play an important role in the processing of colour. Interblobs receive inputs from only the parvo system and seem to process fine patterns in the stimulus. Layer 4b is a subpart of one of the six layers of V1. Its input is solely from the magno system and these cells seem to respond to motion and very low contrast. Thus, the two parallel pathways have now divided into three pathways.

3.3.6.1 V1 Cortical Columns

An important anatomical property of the cortex is its columnar organization. The term "cortical column" refers to the notion that cells arranged vertically from the surface of the cortex to the white matter might comprise functional or anatomical units. Thus, a cortical column can be defined on the basis of anatomical features (e.g. stereotyped patterns of pyramidal cell apical dendrite bundles), functional features (e.g. columns of cortical cells all responding to the same stimulus orientation) or both.

Many types of columns have been proposed including ocular dominance (see example below – Figure 3.11), orientation, spatial frequency, and colour columns (see example

of ocular dominance columns below). Hypercolumns are those columns that contain all the apparatus needed to process input from a specific retinal area. Such columnar organization has important applications in the parallel processing of information in the cortex.

3.3.6.2 Ocular Dominance Columns

Visual signals from the two eyes remain segregated in the LGNd (Figure 3.9- see anatomy of LGNd above) and in the geniculo-recipient layers of area V1 (Figure 3.10). One can observe this segregation by measuring the electrophysiological responses of the units in layer 4C. As the recording electrode is moved within layer 4C, there is an abrupt shift as to which eye drives the unit. In layer 4C, the shift from one eye to the other takes place over a distance of less than 50 microns. Signals from these bands converge on individual neurons in the superficial layers of the cortex, thereby forming columns dominated by one eye or the other in an alternating fashion (Horton et al, 1990)

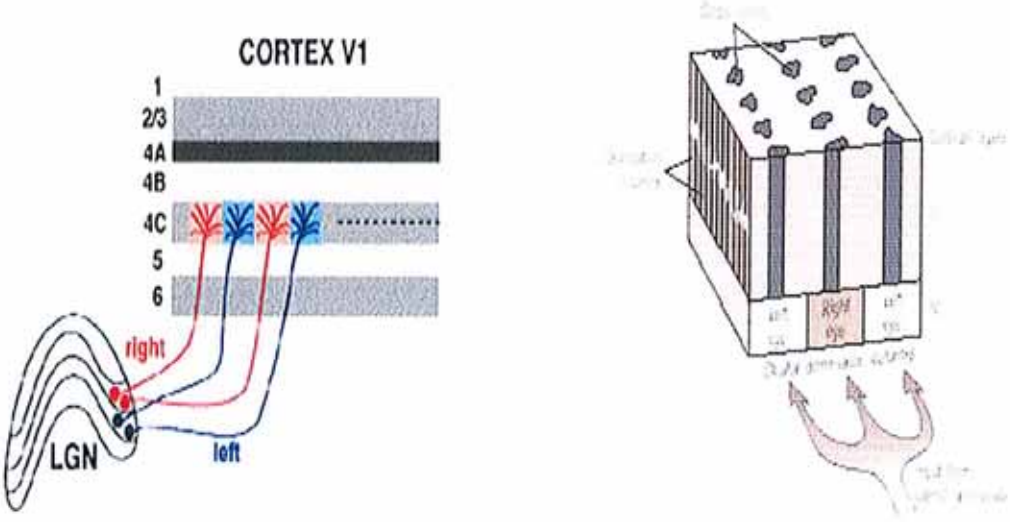


Figure 3.10: The signals from each eye are segregated into different ocular dominance columns within area V1, layer 4C. Orientation columns respond to particular orientations. From: http://dericbownds.net/ bom99/Ch08/Ch08-5.gif

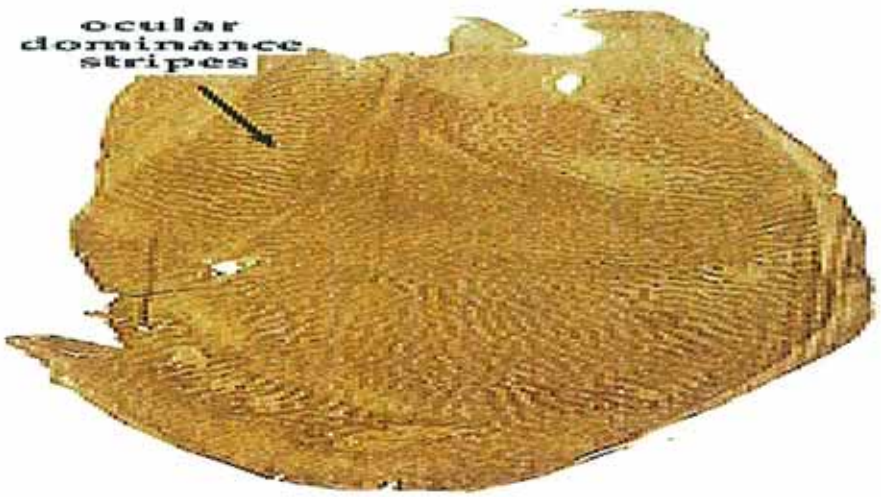


Figure 3.11: The ocular dominance columns in area V1 (layer 4c) can be visualized by using markers. The marker locations (light and dark bands) in this tangential section reveal the ocular dominance columns for the right and left eyes. From: Olavarria & Van Essen (1997).

3.4 Physiology of Visual Processing

The cascade of biochemical reactions and electrophysiological changes that occur when a photon of light is captured by the retinal photoreceptors result in the delivery of an electrical impulse to the visual cortex that facilitates visual perception. A description of such events is less important in the context of this chapter than to outline the various stages and strategies for visual processing whereby the visual system makes sense of the multitude of action potentials traversing the visual pathway resulting in perception as we know it.

The visual system employs numerous anatomical and physiological strategies including lateral interactions between cells, specific receptive field organisation, spatial retinotopic organisation in retinal and non-retinal areas of the pathway, colour opponency and parallel visual pathways among others in order to achieve an instantaneous (stable and constant), yet coherent and highly detailed perception of the outside world and our position within it. Such image processing is not exclusive to the

brain but extends throughout the visual pathway beginning at the retina. The eyes and brain are thus inextricably linked with the visual universe. The eyes actively record the form, colour and movements of the world, and the brain moulds these raw perceptions into recognisable patterns.

3.4.1 Retinal Processing

The retina essentially acts as a spatial, temporal and spectral filter of patterns of light striking its surface. Its anatomical structure and functional properties of individual cells determine the type of information extracted from a visual scene and delivered to the brain i.e. the retina restricts the amount of visual information to which the brain is exposed. The retina is a multilayered tissue containing many different classes of neurons (Figure 3.12). These neurons communicate with each other through a multitude of synaptic connections rich in both their diversity and their complexity.

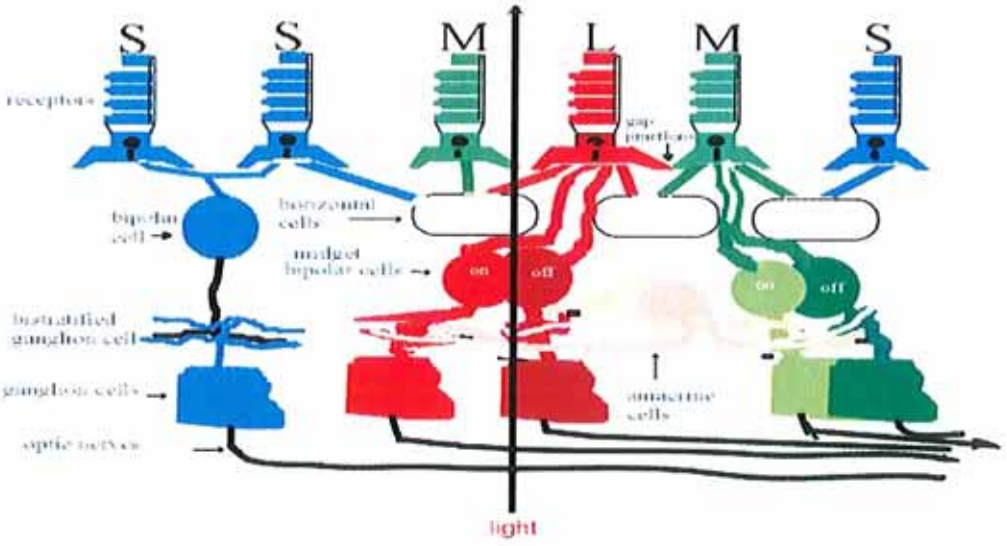


Figure 3.12: Neural retinal feedforward and lateral interactions of short (S), medium (M) and long (L) wavelength cones to on/off bipolar, horizontal, amacrine and ganglion cells. Note lateral interactions of horizontal and amacrine cells. From: http://www.webvision.med.utah.edu/midget.html#connections

Anatomical and physiological retinal design features can account for the type and amount of image processing completed at the retinal level.

- Anatomical observations such as the differential light sensitivity of photoreceptors, variable density and distribution of photoreceptors and ganglion cells across the retina, and the convergence of information in the periphery (Figure 3.13) means that a hierarchy exists in the architecture of retinal processing. Foveal information is given higher priority. This hierarchy continues back to the striate cortex where the vast majority of cortical cells are dedicated to foveal information (Figure 3.16).

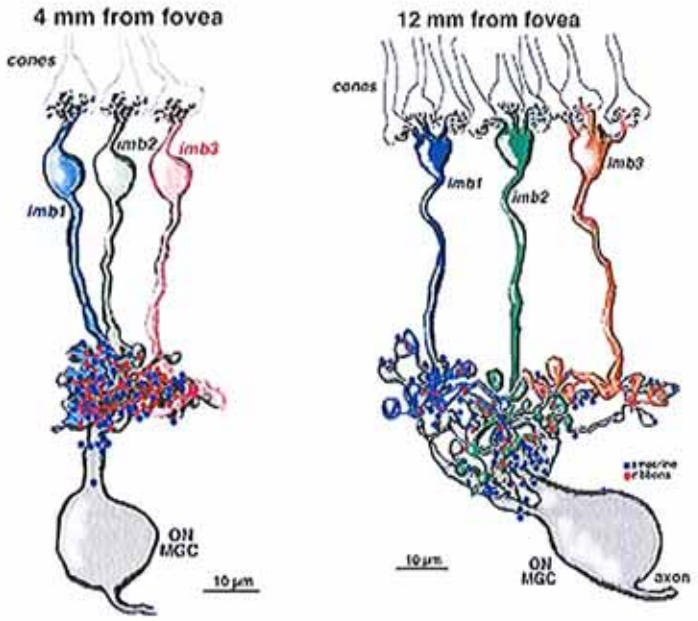


Figure 3.13: Diagrammatic representation illustrating increasing convergence of sensory information at increasing retinal eccentricities. Three cones input to single midget ganglion cell (MGC) via 3 midget bipolar cells (mb) at 4mm eccentricity from the foveal centre, nine cones input to the MGC via 3 mb cells at 12mm eccentricity (Kolb and Marshak, 2003). From: http://webvision.med.utah.edu/imageswv/midget4.jpg

- The spatially antagonistic, centre surround receptive field organisation of bipolar, amacrine and ganglion cells, lateral inhibition networks of horizontal and amacrine cells, transient response of amacrine cells (Werblin & Dowling, 1969), and ganglion cell functional organisation into parvo, magno and konio pathways (Figure 3.14) all serve to modulate information transfer down the visual pathway

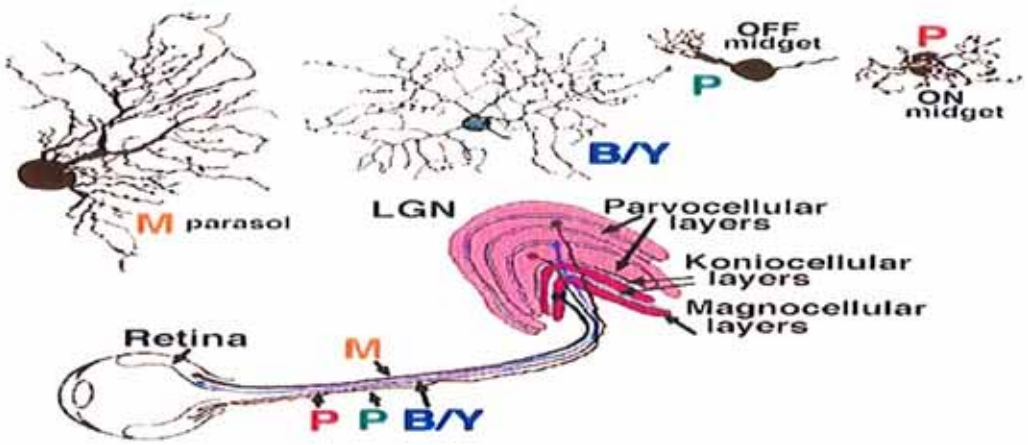


Figure 3.14: Retinal M-, P-, and K-cell retino-geniculate pathways and ganglion cell types. M = Magnocellular, P = Parvocellular (Green colour = mid-spectrum colour responsive; Red colour = low-spectrum colour responsive), B/Y = Koniocellular. Modified from www.krasnow.gmu.edu/.../ Psyc372_01/Cla6.html

The requirement for activation of the various neurons increases as the signal passes through the retinal layers. The selective sensitivity of certain cells to specific stimuli along with the processes of lateral inhibition and information prioritisation through convergence and foveal hierarchy thus modulate the message passed to the LGNd.

What is the point? Well, our entire visual system exists to see borders and contours. We see the world as a pattern of lines, even things as complex as a face. We judge colours and brightness by comparison, not by any absolute scale. This system of lateral

inhibition in the retina is the first step towards sharpening contours and picking up on borders between light and dark. Mach Bands are a perceptual example of this edge enhancement causing exaggeration of the borders between light and dark. Diffuse light is ignored by the ganglion cell, but a sharp dot will really turn it on. Higher up in the cortex, all these dots will be combined into lines, which will be combined into curves, etc. The reasons behind such early image filtering are open to debate. Once information is discarded it can no longer influence perception, so it might be presumed better to transmit all the information to higher levels and allow later stages the flexibility to create any specialised transformations that they need. This obviously does not happen. One reason might involve the architecture that would be required to fully process an image. The ratio of photoreceptors to ganglion cells of the fovea would need to be maintained in the periphery (peripheral spatial resolution decreases at a rate similar to the rate of decrease of ganglion cell density – Lennie et al., 1990). This would necessitate a larger optic nerve that would limit eye movement and cause a significantly larger blind spot. The optic nerve bottleneck is an obvious reason for image processing in the retina. The topographically organised representation of the visual field in the cortex would also need to be vastly increased were more information delivered to the cortex. It has been estimated that the cortex would need to be 50% larger if the optic nerve size was doubled (Van Essen & Maunsell, 1980) to maintain the topographical organisation. One could therefore argue that imposing selectivity early (thereby encouraging development of parallel pathways) limits the load on central mechanisms (Lennie et al., 1990).

3.4.2 Processing in the LGNd

The LGNd, as already mentioned, is a relay station between the retina and striate cortex. It is however, somewhat involved in further processing the image information it receives prior to transmitting it along the optic radiations (Lachica & Casagrande, 1993), and also in preserving the retinotopic neural organisation to facilitate cortical processing.

The receptive field organisation of geniculate neurons in the different layers closely resembles that of the retinal ganglion cell inputs to those layers e.g. concentric and antagonistic centre-surround, achromatic or spectrally-tuned etc. Response profiles of geniculate neurons however can be different, indicating that the LGNd acts as a regulator or filter of visual information passing to the cortex (Hubel & Wiesel, 1961; Kaplan et al., 1987). Also, only 10-20% of synapses onto geniculate neurons are from retinal input. Nearly 50% arise from descending inputs from the cortex, and the remainder from local inhibitory and brainstem inputs. These non-retinal inputs appear to provide a switch for the relay of information, and the LGNd therefore, is best seen as a dynamic filter regulating passage to the cortex (Sherman, 1996).

Ganglion cells are divided into two primary classes first identified by Gouras (1968). It has become common to refer to the ganglion cells based on their projections to the dorsal LGN of the Thalamus, to which almost all retinal ganglion cells project (DeMonasterio & Gouras, 1975). In this way, ganglion cells are identified as M-cells if their axons project to the 2 more ventral layers, the magnocellular layers of the LGNd, which are composed of larger cells. They are identified as P-cells if they project to the 4 more dorsal layers, the parvocellular layers of the LGNd which are composed of smaller cells. The majority of cells fall into these two categories, and along with their

LGNd counterparts, they are both morphologically and physiologically distinct. These cells form the basis for the parallel visual system for information processing. (see section 3.4.3).

The segregation of cells within the LGNd extends further than just based on cell type. The spatial position of ganglion cells within the retina is preserved by the spatial organisation of the neurons within the LGNd layers. Because of the hemi-decussation that occurs at the chiasm, each LGNd receives input from both eyes, from the nasal field (temporal retina) of the ipsilateral eye, and the temporal field (nasal retina) of the contralateral eye. Each of the magnocellular and parvocellular layers receives input from only one eye: Layers 1, 4 and 6 receive fibres from the contralateral nasal retina, while layers 2, 3 and 5 receive input from the ipsilateral temporal retina (DeMonasterio & Gouras, 1975).

Each layer of the LGNd contains a retinotopic map or representation of the contralateral hemifield of vision. Such a map serves as a point-to-point localisation of the retina whereby neighbouring regions of the retina project to adjacent regions within each layer. These maps are stacked on one another such that if a line (called a line of projection) were passed through all six layers, the intercepted cells would all be carrying information about the same point in the visual field (Casagrande & Ichida, 2003). Thus the fibres carrying information about the same position in the visual field of each eye terminate in adjacent layers of the LGNd, right next to one another (Warwick, 1976).

The maps however are not uniform representations of the visual field. The central field is particularly well represented, reflecting the different densities of ganglion cells

across the retina. Thus, the LGNd translates the much greater foveal/parafoveal ganglion cell density into a greater spatial representation which is then carried to V1 where the majority of cells are devoted to foveal vision. The posterior LGNd contains neurons whose receptive fields are near the fovea. Progressing from posterior to anterior, the receptive field locations become increasingly peripheral in the retina (Erwin et al., 1999). In summary, the LGNd contains a number of overlapping maps of the retina which arise from different ganglion cells types with different response properties (Oyster, 1999).

3.4.3 Parallel Visual Pathways

Numerous authors have provided evidence about the functional connectivity of retinal ganglion cells to LGNd neurons (DeMonasterio & Gouras, 1975; Perry et al., 1984; Schiller & Malpeli, 1978; Leventhal at al., 1995). Results show that when the parvocellular layers of the LGNd were injected with horseradish peroxidase, a population of retinal ganglion cells with small cell bodies, axons and dendritic fields were labelled retrogradely. These small ganglion cells were densely packed especially near the fovea. Cell counts indicate that these P-cells comprise approximately 80% of the ganglion cells that project to the LGNd. Injections into magnocellular layers labelled a completely different population of ganglion cells with large cell bodies, axons and dendritic fields. They were more sparsely packed in the retina and comprised about 10% of ganglion cells projecting to the LGNd (Lennie et al., 1990).

Direct electrophysiological evidence about retina to LGNd connectivity in primates comes from Kaplan and Shapley (1982) who recorded excitatory synaptic potentials (from retinal ganglion cells) extracellularly in different LGNd layers and found that different types of retinal ganglion cells drive different LGNd layers.

Electrophysiological (Livingstone & Hubel, 1987b) and psychophysical (Lee et al., 1990; Schwartz, 1993) probing of these pathways has revealed that the visual functions associated with the magno and parvo pathways of vision also allow us to distinguish them as separate pathways. Behavioural studies in monkeys illustrate the functional segregation of these pathways. Lesions of the parvo layers produce predictable reductions in contrast sensitivity for high spatial frequencies and wavelength based discrimination ability but high frequency flicker detection remains unaltered (Merigan, 1989; Schiller et al., 1990 a & b). Lesions in the magno pathway cause a profound reduction in flicker detection but no effect on wavelength based discrimination or high spatial frequency resolution (Merigan & Maunsell, 1990; Schiller et al., 1990 a & b). Table 3a below outlines the basic differences between the two pathways.

FUNCTION	MAGNO	PARVO
Acuity	No	Yes
Colour Discrimination	No	Yes
Spatial Resolution	Low spatial frequency	High spatial frequency
Temporal Sensitivity	High temporal frequency	Low temporal frequency
Temporal Responsiveness	Transient	Sustained
Speed of Transmission	Fast	Slow
Spatial Linearity	Linear or Non-Linear	Linear
Retinal Distribution	Peripheral	Central

Table 3a: Characteristics of parvo and magno neurons of the retino-geniculate pathway. (Schwartz, 1994).

Both M and P-cells have concentric, antagonistic centre surround organisation with the receptive field size of parvo cells smaller than magno cells. P-cells respond in a more sustained fashion and their axons have a medium conducting velocity-13m/s average.

M-cells respond more transiently and have rapid conduction velocities-21m/s average (Lennie et al., 1990). Because magno cells respond transiently, they can respond to rapid changes in illumination and therefore are able to resolve high temporal frequency stimuli. The sustained parvo cells continue to respond while the stimulus is temporally stable and are therefore able to code low temporal frequencies (Derrington & Lennie, 1984).

The P-cell pathways are responsible for processing chromatic information, especially for the short wavelength cone system. They are colour opponent meaning that the responses of P cells to stimuli that fill their entire receptive field change sign dependent upon the wavelength of the stimulating light i.e. (excitation to inhibition). M-cells are thought to be spatially broadband, giving the same sign of response to all wavelengths of light. Some M cells however are colour opponent. These cells are excitatory for the LGNd neurons called Type IV cells. They have an excitatory receptive field centre mechanism that is broadband and an antagonistic inhibitory surround that is selectively sensitive to long wavelength red light.

Besides their spectral sensitivities, conduction velocities and response time course, another property that distinguishes P from M cells is contrast gain, which is the change in response of the neuron per unit change in contrast. As a function of contrast, the neural response grows much more steeply for the M cell than the P cell especially at low contrast. The parvo and magno pathways are the conduits for signals about detection of contrast. The high gain M system is most suited to handle detection of grating patterns of low to medium spatial frequencies (<20cyc/deg) and at low luminance. The numerous P cells may be required to accurately represent the fine

spatial grating patterns near the acuity limit and at high luminance (Kaplan & Shapley, 1982; Derrington & Lennie, 1984).

Purpura et al. (1988) indicate that P cells become visually unresponsive to grating patterns when the mean luminance drops below 0.1cd/m2 at the rod/cone break. M cells also become progressively less sensitive as mean luminance is reduced, however, because they are much more sensitive, they remain responsive in the scotopic range.

Thus, in general we see that cells in the magnocellular pathway are most sensitive to high temporal frequencies, low spatial frequencies, high luminance contrast and movement. They are not colour opponent but do handle some colour processing. Cells in the parvocellular pathway respond best to low temporal frequencies, high spatial frequencies and are colour opponent.

There is still some debate as to whether the two pathways are independent. The varying sensitivities of individual cells probably mean that there is some degree of overlap between the two. Merigan and Maunsell (1993) concluded this way: "We expect that the question of parallel pathways will continue to generate intense interest, and it is likely that our understanding will be refined in coming years. Whatever consensus emerges...the simple description that has held sway in recent years is, at best, a rough approximation of the truth".

3.4.4 Cortical Processing

The first stage of cortical processing of visual information occurs in the striate cortex, the primary target site for projections from the dorsal LGN (see Scetion 3.4.2 above). Fundamental aspects of visual analysis occur within the striate cortex. From here, visual information is disseminated through the cortex (Figure 3.15) to the more than

thirty defined exclusively visual centres (De Yoe & Van Essen, 1985; Van Essen et al., 1992), and also on to other areas where it is integrated with memory and other senses. Anatomical hierarchical models place the visual cortical areas into a multi-level processing model based upon the pattern of feedforward, lateral and feedback pathways found in each area (Felleman & van Essen, 1991; Hilgetag et al., 1996; Barone et al., 2000) – see figure 3.15.

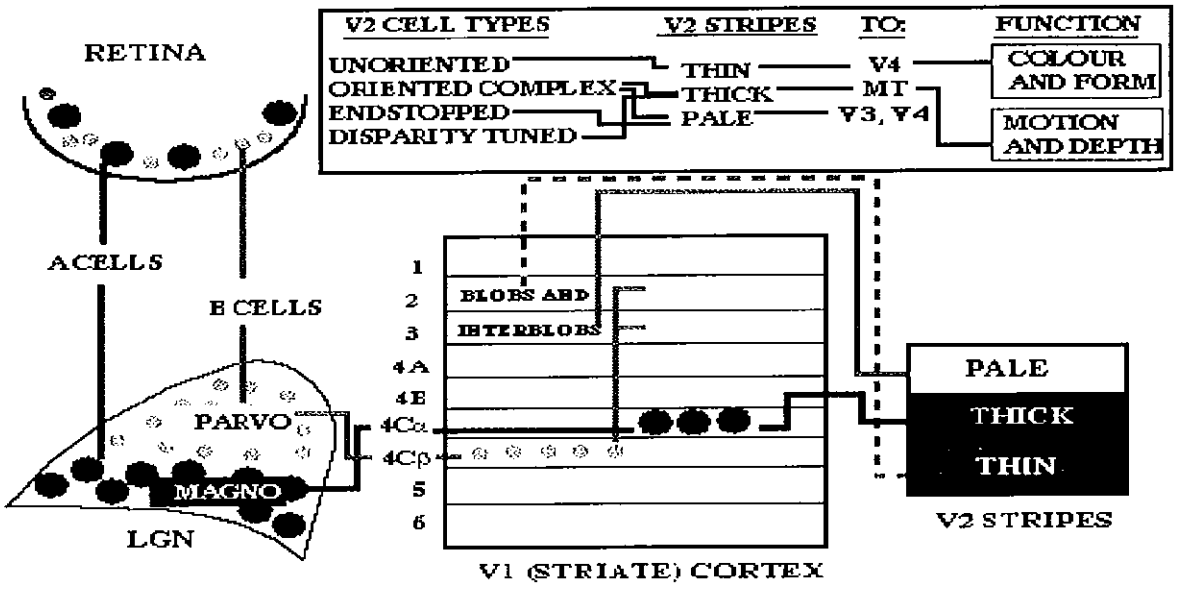


Figure 3.15: Model of parvocellular (small, sustained, X-like cells) and magnocellular (large, transient, Y-like cells) streams in the primate visual pathway, from the retina via the lateral geniculate nucleus to V1 then V2 visual cortex, and then on to other extrastriate areas.

From: http://vision.bhs.mq.edu.au/.../ corella/237/outl7.html

Information travels along the visual pathway from the retina to the LGNd to V1 and on to higher cortical areas and higher cortical areas project back to V1 and V1 to the LGNd (there are no efferent projections to the retina). However such a basic description does not even begin to capture the wealth of upstream, downstream and extensive lateral connections within and beyond V1. What is

more important in this context is to provide a basic description of how the anatomy and physiology of the cortex facilitates visual processing.

The question thus arises, how does the visual cortex resolve the millions of patterned electrical spikes into visual consciousness? The basic answer lies in analysis of what information the electrical signals actually carry, the specialised selectivity of cortical neurons, the receptive field properties and retinotopic organisation of V1 and V2, the anatomical laminar and columnar organisation of V1 and finally the extensive neural links between multiple visual areas and importantly, links to other areas of the brain for motion processing and integration with memory etc.

3.4.4.1 Retinotopic Maps

The retinotopic map is maintained to varying degrees in the visual cortex. Just like the mapping of the contralateral hemifield in the LGNd, the axons of the geniculo-cortical pathway convey this map into the cortex. The map again is not uniform, with the central retinal pathways having by far the greatest proportion of the representation (estimates range from 37% of the cortex devoted to the central 15 degrees (Wong & Sharpe, 1999) to 87% of the cortex devoted to the central 30 degrees (Horton & Hoyt, 1991 – see Figure 3.16).

Therefore, corresponding points from the two retinas (ipsilateral temporal and contralateral nasal) that represent the same target in the visual field will project to the same place in the primary visual cortex. Precise retinotopic maps are maintained in V1 and V2. Subsequent cortical areas have representations of the visual field but not nearly as precise as those of V1 and V2.

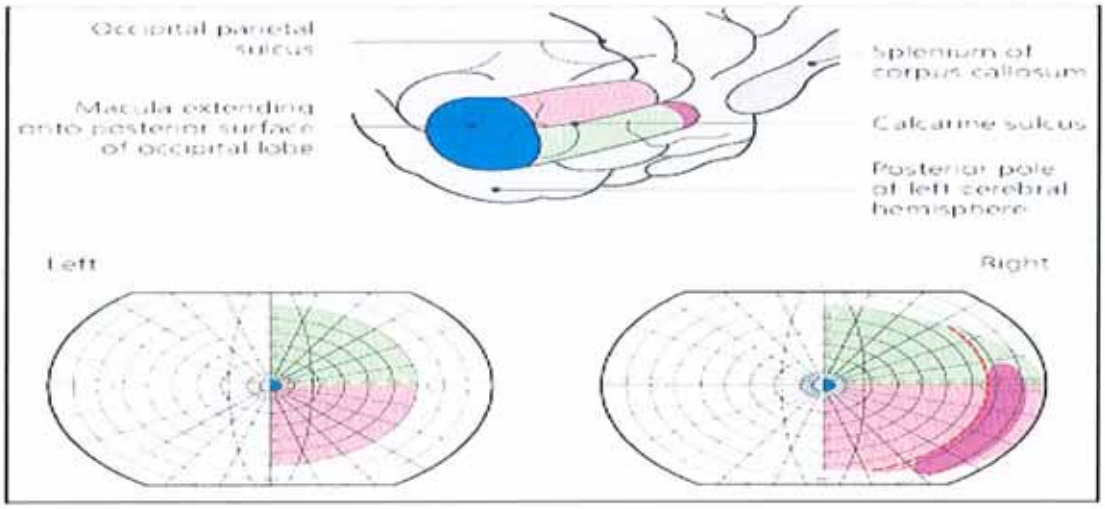


Figure 3.16: Illustration of the cortical representation of central and peripheral visual fields. Macular fibres, whose spatial representation is grossly enlarged, terminate in the most posterior striate cortex. From: Spalton et al, 2005; p667.

The aforementioned feedback loops, backward or reentrant connections from higher cortical areas to V1 are not well understood but one possible role for them is to index the processing in V3, V4 and V5 to the more precise visual maps found in V1 and V2. Although each of the visual regions has a map of the visual world, they are not nearly as precise and detailed as those found in V1 and V2. In other words, their receptive fields are much larger which allows for poorer localization of a stimulus or object. For example, although V4 locates a colour region in space, the receptive field is rather large and might not indicate whether this colour belongs to the cup or the book on the table in front of you. These reentrant connections, feeding back to the precise maps of V1 and V2 may provide a mechanism that allows the visual system to assign the colour precisely to the appropriate location and object, say a part of the cover of the book in front of you.

3.4.4.2 Columnar Organisation

The columnar organisation of the cortex described in section 3.3.6.1 dictates that all cells in a cortical column respond to a stimulus presented at a particular point in the

visual field, and cells in adjacent columns respond to a point in the adjacent visual field (Hubel & Wiesel, 1968). One column processes oriented stimuli of a certain width from a certain location on the retina; the next column processes stimuli with a slightly different orientation. Each column is organised in a parallel fashion processing information simultaneously.

It is also known that such cells also have an optimal response to stimuli with the same axis of orientation (termed orientation columns). The vast majority of V1 cells show some degree of orientation selectivity (Hubel & Wiesel, 1968), and approximately 25-35% of V1 cells are also strongly directionally selective (Schiller et al., 1976; DeValois et al., 1982). This concept can be elaborated further to account for the detection of movement (V5 cells specialized for motion and stereopsis detection) and colour (V4 cells are colour selective –Sacks & Wasserman, 1987; Zeki, 1990) for example in other cortical areas.

Other cells have been shown to respond preferentially to visual stimulation in both eyes (Hubel & Wiesel, 1962). Such cells are responsible for our ability to detect binocular disparity and therefore underpin stereopsis.

3.4.4.3 Specialised Pathways

Not only are cortical cells specialised for selective sensitivity, there also exists evidence of separate definable specialised pathways in cortical processing. Dubner & Zeki's (1971) discovery that the bulk of neurons in the middle temporal area (MT or V5) were strongly directionally selective has suggested its possible role in motion processing. V5 receives its main direct inputs from layer 4b (Maunsell & Van Essen, 1983) and layer 6 (Fries et al., 1985) of V1, and indirect inputs via the thick stripes in V2 (DeYoe & Van Essen, 1985) and also from V3. These projections are intimately

linked to the fast conducting magnocellular pathway. Numerous studies have also shown that neurons in V5 respond optimally to the movement of complex patterns (Newsome et al., 1985; Movshon et al., 1985; Newsome & Pare, 1988).

Zeki (1981) described the pronounced chromatic selectivity of cells contained in V4. Subsequent studies have confirmed the involvement of V4 in colour processing (Schein et al., 1982; Desimone et al., 1985). Some of the properties of neurons in V4 are also important in the perception of colour constancy. The large receptive fields and colour opponent organisation could help discount changes in the spectral composition of the illumination falling on a scene, and thereby contribute to the stable appearance of coloured objects (Zeki, 1983). V4 does have a somewhat ambiguous role however in that it receives input from the interstripe regions of V2 which have spatially elaborate receptive fields and is therefore involved in spatial vision (Heywood & Cowey, 1987), and from V3 which contains relatively few neurons that show overt colour opponency.

3.4.4.4 "Where" versus "What"

There is converging evidence from clinical neurology and experimental physiology that higher cortical areas fall into two groups, one particularly concerned with locating objects "the where system" and the other with identifying them "the what system" (Ungerleider & Mishkin, 1982; Mishkin et al., 1983; Maunsell & Newsome, 1987; Livingstone & Hubel, 1987b). These constellations of areas appear to diverge beyond V2 and V3- (Figure 3.17).

The temporal "what" pathway or ventral processing stream runs toward the inferior temporal cortex, an area where damage can disrupt the ability to recognise objects

(Mishkin et al., 1983; Damasio, 1985), and receives its predominant input from the P pathway. The parietal "where" pathway or dorsal processing stream runs into the superior parietal cortex, a region known to be involved in space perception (Ungerleider & Mishkin, 1982). Feedback from these areas may link the "where" and "what" information into the precise V1 retinotopic maps. Although information is parcelled out along the temporal and parietal pathways, there is substantial communication between them so they are not independent pathways.

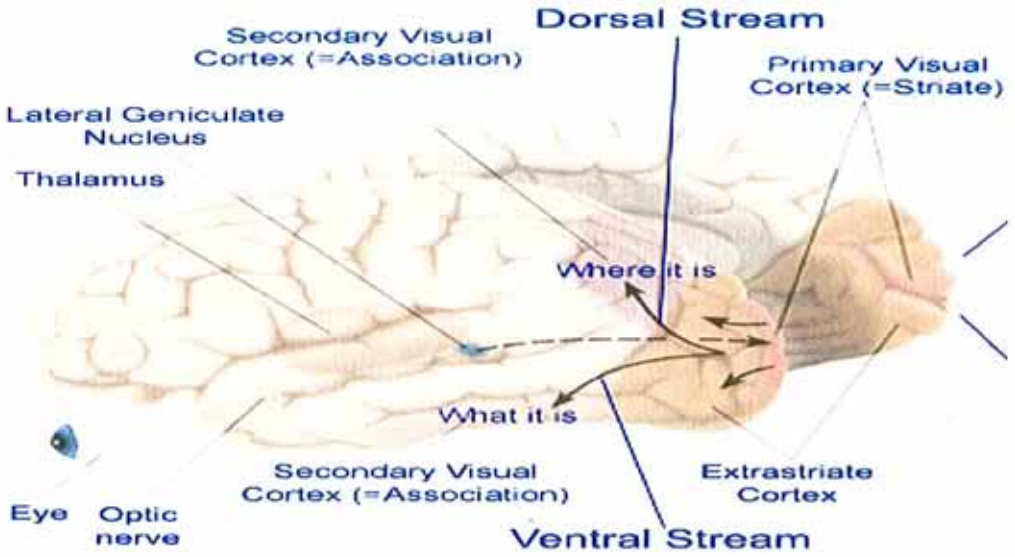


Figure 3.17: Where and what extrastriate pathways. From: www.homepage.psy.utexas.edu/.../Vision/13.gif

The anatomic and physiological organisation of the cortex (while much more complex than presented here) thus provides the architecture for analysing the individual components of a scene.

3.5 Physiology of Preattentive Visual Search

The idea that the brain operates with many parallel elements is the major emerging theme in our present understanding of the neural bases of the sensory systems; different pathways and different modules of the sensory systems operate to extract

unique features of the information in the sensory stimulus. Throughout the sensory systems, there is evidence of parallel (that is simultaneous) operations, both with parallel pathways and parallel targets for sensory information.

Sensory information processing was first viewed as predominantly serial (that is sequential), based upon the groundbreaking work of Hubel and Wiesel (1962, 1968). However, even in these early studies researchers began to find evidence of parallel processing, with Hubel and Wiesel themselves uncovering the existence of cortical columns.

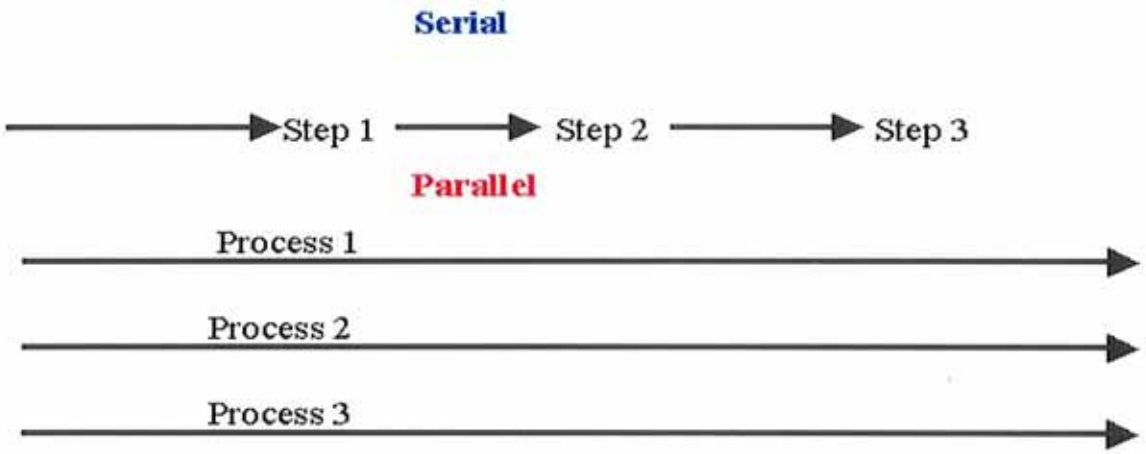


Figure 3.18: An illustration of the difference between serial and parallel processing. Serial processing is in stages and parallel processing is different processes proceeding at the same time. From: http://teachpsych.lemoyne.edu/teachpsych/faces/script/Ch09_HTM/visual_neuroscience.htm

Another important early finding that foreshadowed today's emphasis on parallel processing was the discovery of X and Y cat retinal ganglion cells by Enroth-Cugell and Robson (1966). The differential sensitivities and response patterns of such cells (Figure 3.19), which have been extended and adapted to primate M and P cells, clearly

indicate that there is something fundamentally parallel in the processing of visual information.

Studies by Hubel and Wiesel (1968) found a similar functional segregation in the cortex between their simple and complex cells although at the time they interpreted these cells as sequentially linked.

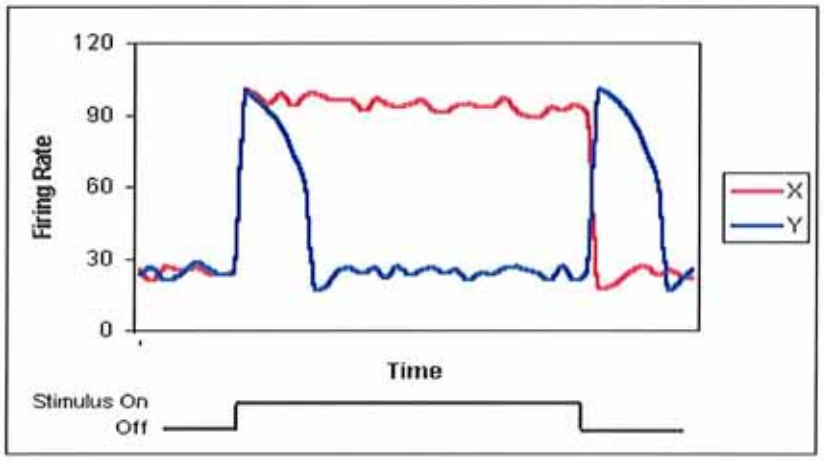


Figure 3.19: Response patterns of X and Y cells. X cells exhibit a sustained response to a stimulus, while Y cells respond transiently to stimulus onsets and offsets. From:

http://teachpsych.lemoyne.edu/teachpsych/faces/script/Ch09_HTM/visual_neuroscience.htm

Our present understanding of the visual system is very different from the serial model Hubel and Wiesel initially proposed. There are separate functional modules that operate relatively independently; information, instead of flowing in one direction, now flows in both directions. Thus, later levels do not simply receive information and send it forward, but are in an intimate two-way communication with other modules. The anatomical and physiological work so far completed provides only modest hints about

the dimensions along which an image is analysed. The parallel analysis of the image is valuable because it enables the rapid assembly of percepts (Figure 3.18).

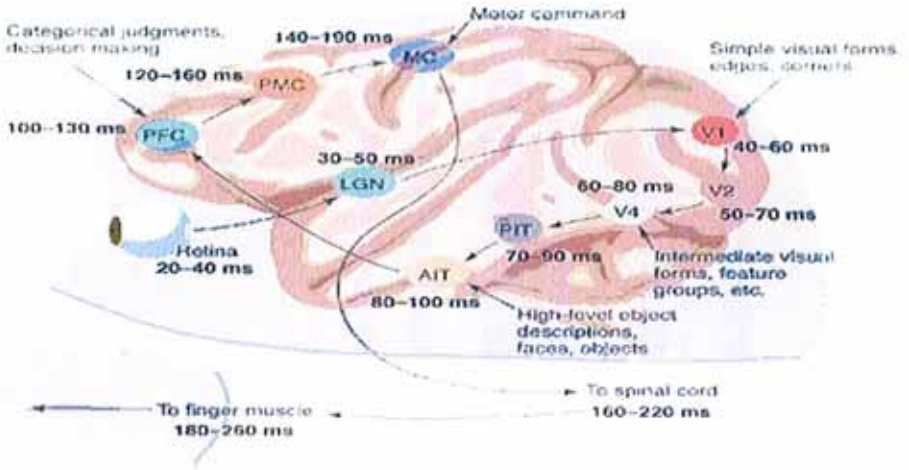


Figure 3.20: Pathway timing from retinal stimulation to motor response. A motor response to a retinal stimulus can be initiated in as little as 180 milliseconds. From: www.owlnet.rice.edu/ ~psyc351/imagelist.htm

Our sensitivity to specific visual field locations is known to be modulated by attention (Posner & Petersen, 1990; Desimone & Duncan, 1995; Maunsell, 1995). Spatial attention should be differentiated from other forms of attention such as attention to objects or features. Because spatial attention is so dynamic yet localised, it has often been described in metaphors such as a "spotlight" (Treisman & Gormican, 1988) of attention, while others regard such top-down metaphors as misleading, instead viewing attention as an "emergent process" (Desimone & Duncan, 1995).

Neurophysiological results appear to support a hierarchical model of visual spatial attention in which spatial attention is, ironically, least prominent in V1, the area of most precise retinotopic representation. Instead, spatial attention is thought to modulate activity in higher-order areas (e.g. MT) where receptive fields are much larger (Moran & Desimone, 1985; Mangun, 1995; Culham et al., 1998). Spatial

attention preferentially activates parietal cortical regions connected to the dorsal "where" stream such as MT and V3A (Culham et al., 1998; Tootell et al., 1998).

In daily life, attention is thus drawn to a specific location in the visual field following the early, rapid and parallel processes of visual processing, in particular that of the magnocellular dorsal stream to detect the location (approximate) of interesting objects in the visual field.

Attentional capture is followed, almost immediately by a saccade to the relevant location in the visual field. Such parallel processes extract the basic features of the scene but object recognition generally requires subsequent serial attention mediated by the parvocellular ventral stream (Figure 3.21). A motor response to a visual stimulus can be initiated in as little as 180 milliseconds (Figure 3.20 - Schmolesky et al., 1998; Nowak & Bullier, 1998) based solely on the outcome of such parallel processes without the direct requirement for object identification.

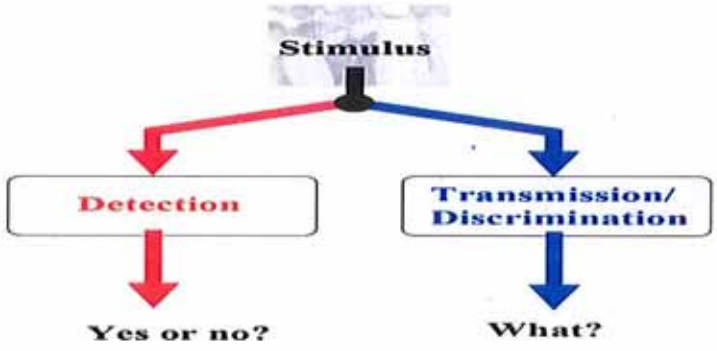


Figure 3.21: Dual image processing strategy to detect then discriminate objects. From: www.people.deas.harvard.edu/.../transmit_detect.jpg

In certain contexts, it is important for the visual pathway to transmit fine details concerning features of the outside visual world. We may think of this as the "what" question: given that something of interest is in my visual field, what is it? Is it predator

or prey, or perhaps a potential mate? In other ethologically relevant contexts, it is important to detect the presence of an object or to signal novelty, in a "bottom-up" context, potentially for the "top-down" allocation of attentional resources. We may think of this as a *yes or no* question: is something of interest there or not? The fast and robust detection of changes in the external environment may be critical for survival. The startling aspect of this dichotomy is that the seemingly disparate tasks are in fact accomplished by the same neuronal circuitry.

Parallel processing does impose conceptual difficulties however. How is the information contained in the separate representations brought together to yield unified experience of the visual world? How large is the spotlight of attention across the cortical map in each visual area? These and other questions remain to be answered.

In summary, what we see can be divided into several categories of vision: colour, linear pattern, motion, etc. The integration and perception of these different categories requires a wide variety of anatomical and physiological strategies such as retinotopic maps, space variant processing (cortical magnification), hierarchy, laminar and columnar organisation, feedback and lateral interactions, selective sensitivity and parallel processing. The two types of information, motion versus colour and form, are maintained in separate compartments all the way up the visual pathway. They are kept in separate layers in the LGN, enter V1 via separate sublayers (4Cα and 4Cβ), and after passing through V2, go on to separate areas of extrastriate cortex. In the end, the parietal visual cortical areas (such as MT and PP) end up dealing with motion of objects, navigation through the world, and spatial reasoning (which is essentially moving things around in your head). Temporal visual areas (such as V4 and IT) are involved with the complex perception of patterns and forms as recognizable objects.

So when Aunt Nellie goes streaking by you as your usually docile dog Cujo gives chase, your motion pathway will instantaneously tell you which way she went, and your colour/form pathway will identify her as Aunt Nellie. Any emotional response you attach to this event will be mediated by the amygdala, incidentally.

3.6 Conclusion

The organisation of the brain is such as to create "abstractions", rather than to simply take input at face value. A checkerboard is a checkerboard is a checkerboard not because the input reaching our eyes is the same at all times but rather because the nervous system is organised to reject some information and replace it with other information. The confusion of the external world is rendered stable and comprehensible by the organisation of the nervous system. That organisation represents information added by the nervous system to the information it receives, and constitutes a presumption that there exist stable, constant external forms with well-defined boundaries. The presumption is strong enough so the nervous system actually creates boundaries where none in fact exist.

Such a presumption probably reflects genetic information (the experience of innumerable generations of ancestral organisms) about the nature of "reality", and might be absent in organisms evolving under other circumstances where they do not interact with stable, constant, spatially bounded external forms. Such presumptions also probably provide a basis for the human experience of "ideal forms". Such "ideal forms" are not, as Plato might have imagined, properties of the real world dimly glimpsed by imperfect humans, but rather abstractions created by the brain. Such abstractions are properties of the "unconscious" rather than the "conscious" parts of the brain. The visual information that reaches the eye cannot uniquely describe the

physical world. Because light arising from different physical objects can stimulate the retina in the same way, the source of a light stimulus is inevitably ambiguous. For example, a large object far away and a small one closer by can generate exactly the same retinal image. The visual port of the brain resolves this ambiguity by assigning appropriate values of brightness, colour and geometry to the things we see. Purves & Lotto (2003) argue that this assignment is made on a wholly probabilistic basis: What observers see in any circumstance is simply what the stimulus has typically signified in the past, indicated by behavioural success or failure.

CHAPTER 4

GLAUCOMA

4.1 Introduction

Glaucoma is the end result of a group of disorders specific to the eye. It is one of the leading causes of blindness in the developed world (Quigley, 1996), and is of increasing public health concern due to our aging population demographics (glaucoma, along with other leading causes of blindness is more prevalent among the elderly – Tielsch et al., 1991; Klein et al., 1992; Quigley et al., 2001). It causes blindness because this condition results in a predictable but irreversible pattern of retinal nerve fibre bundle loss (Figure 4.1).

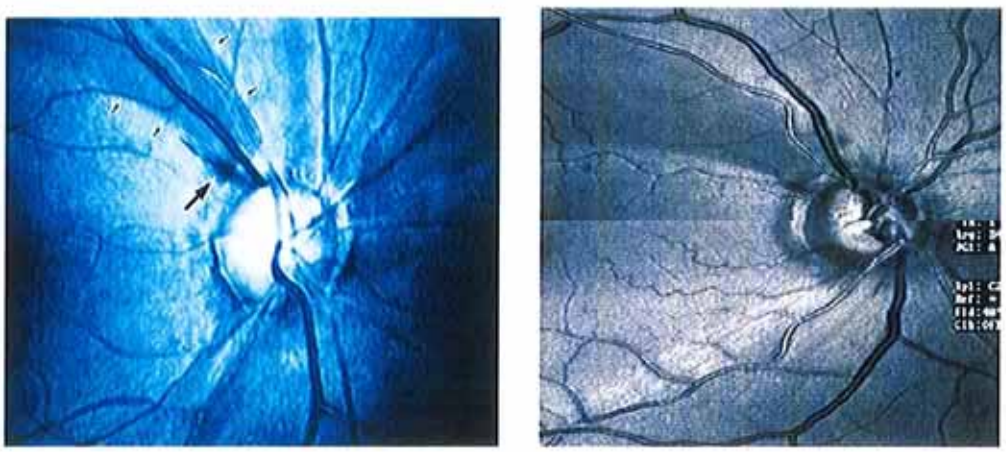


Figure 4.1: Superior arcuate nerve fibre defect associated with superior neural rim notch. From: http://www.oftalmo.com/seo/2003/01ene03/05.htm

As the retinal ganglion cells die, the portion of the patients' visual field they serve is lost. Peripheral vision is characteristically affected prior to detailed foveal vision. Early losses have minimal visual impact and patients therefore remain largely asymptomatic and unaware of its presence. This however means that a significant percentage of patients go undiagnosed in the early stages (Coffey et al., 1993). Most epidemiological studies estimate that approximately 50% of people with glaucoma are as yet undiagnosed (see section 4.15).

This has repercussions for the ultimate prognosis, as treatment success is crucially dependent on the extent of the damage at initial diagnosis (Grant & Burke, 1982; Wilson et al., 1982; Tezel et al., 2001). Untreated glaucoma leads to progressive field loss until ultimately only a small central island of vision remains. Even if we are painfully aware of what glaucoma does, we have to admit that we do not yet fully understand what glaucoma is.

4.2 Historical Perspective on Glaucoma

The German Ophthalmologist, Albrecht von Graefe, who first identified glaucoma defined it as follows- "The semeiotic concept glaucoma is rooted in the increase of intraocular tension, which has repercussions on the functions of the optic nerve and retina", (Heilmann & Richardson, 1978; Sommer, 1989). Observations such as the apparent increase in the prevalence of open angle glaucoma as intraocular pressure increases (Sommer et al., 1991b) and the characteristic neuropathy accompanying the rise of intraocular pressure in induced glaucoma in monkeys have led to the "logical" conclusion that raised intraocular pressure was the root cause of glaucoma.

Ever since, glaucoma has been inexorably linked to increased intraocular pressure (IOP) in what is assumed to be a cause and effect relationship. As a consequence the diagnosis and therapy of glaucoma seemed almost self-evident: The IOP was to be measured and, if found to be increased, lowered.

Epidemiological studies however have shown that there are about as many cases with a 'normal' intraocular pressure (</=21mmHg), as there are with a high intraocular pressure among glaucoma patients (Hollows & Graham, 1966; Leibowitz et al., 1980; Coffey et al., 1993). Indeed in oriental populations, 'normal' IOP is present in up to

70% of glaucoma cases (Shiose, 1983; Fukunaga et al., 1985; Shiose et al., 1991). Such cases are at odds with the traditional idea of glaucoma as a pressure induced neuropathy. This objection however has been rejected by referring the low-tension cases to a separate group, the so-called 'normal tension or low tension glaucoma' in which the 'normative pressure', i.e., the pressure tolerated by a specific eye, is supposed to be abnormally low. The IOP in such cases is by definition abnormal for the particular eye, and should not be compared to a statistically pre-determined threshold.

The use of a certain pressure level to distinguish chronic simple glaucoma from low-tension glaucoma has no basis in scientific fact. It is absurd to think of two separate diseases occurring just because a single intraocular pressure reading in one of the two eyes happens to exceed an arbitrary limit. These studies have also shown cases with a high intraocular pressure which never develop glaucomatous defects, indeed the percentage of people with high intraocular pressure that go on to develop glaucoma is extremely low, ranging from 0.5 – 5% (Armaly, 1969; David et al., 1977; Leske, 1983). This again tends to cast doubt on a simple pressure theory. These cases are supposed to have 'a high normative pressure', and are termed 'ocular hypertensives'.

The 'pressure theory' had in some ways become immune to falsification.
This determination to invent terminology and seek alternative explanations for seeming inconsistencies is neither scientific nor is it helpful in the quest to better understand the enigma that has become known as 'glaucoma'.The pressure theory has thus lost most of its meaning. What remains is, mainly, a therapeutic tradition-apparently well tried but based on obsolete ideas and, as a matter of fact, often not

shown to be justified by a consistent positive effect of the desired object, which is always the same-a lowering of the intraocular pressure.

It is well known that many glaucoma cases with a controlled IOP, medically or surgically, are seen to develop papillary atrophy and field defects, in spite of apparently successful therapy (O'Brien et al., 1991; Palmberg, 2001; Tezel et al., 2001). Indeed, Hattenhauer at al (1998) have estimated the probability of blindness occurring due to glaucoma to be 27% unilaterally and 9% bilaterally over the course of a twenty-year follow up despite therapeutic intervention (Figure 4.2).

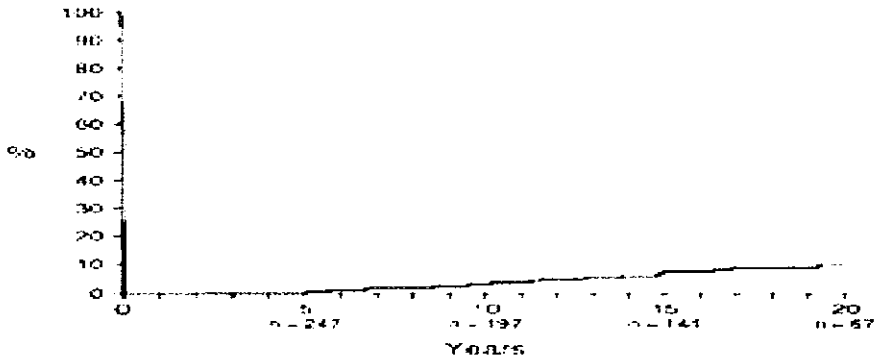


Figure 4.2: The cumulative probability of bilateral blindness from open angle glaucoma estimated at 9% (Hattenhauer et al., 1998).

Ad hoc the opinion is advanced that when defects can be detected it may be too late for efficient therapy. Now the situation becomes paradoxical; when functional defects can be detected, therapy may not stop progression, and as long as no such defects can be detected the diagnosis of glaucoma cannot be established.

4.3 Risk factors in Glaucoma

Despite such reservations as to whether IOP elevation is the root cause of glaucoma, it is still recognised as a significant risk factor in glaucoma, in that significantly elevated IOP will invariably induce glaucomatous neuropathy. Current classifications of the types of glaucoma are actually based on how the IOP is raised and relate in no form to

the damage caused. IOP reduction is also the only "successful" treatment modality currently available for glaucoma management. The ocular hypertension treatment study has confirmed the benefit of treatment of ocular hypertension, more than halving the probability of developing open angle glaucoma (Higginbotham et al., 2004). The correlation is so imprecise however that, other factors must be involved to explain the discrepancy. Since present therapy is designed only to decrease IOP, we should therefore not be surprised that a significant percentage of those patients with heterogeneous (where other mechanisms or combinations of such are the primary cause) glaucomatous optic neuropathy continue to deteriorate despite therapeutic intervention. It therefore becomes obvious that it is damage, and not pressure, which is the important feature of the condition.

While elevated intraocular pressure is an important risk factor for the development and progression of glaucomatous damage, it is still only a risk factor (see Table 4a), along with family history, age, myopia, race, diabetes, vascular disease, pseudoexfoliation, pigment dispersion syndrome, peripheral vasospasm and extracellular matrix anomalies among others, and not the disease itself. Glaucoma is therefore, a disease of the optic nerve that can be impacted by faulty aqueous dynamics and numerous "other factors", and not a disease of faulty aqueous dynamics, i.e. glaucoma is associated with many risk factors but none of these risk factors or combinations of risk factors defines glaucoma. Recent advances in basic science and clinical methods are modifying our thinking about our basic concepts of glaucoma. The definition of glaucoma has evolved in parallel with increased understanding of the underlying disease process. The traditional view that glaucoma is caused by increased IOP has been challenged and indeed IOP is seldom used in modern definitions, including the most recent American Academy of Ophthalmology definition (AAO, 2005).

IOP (Anderson & Hendrickson, 1977; Sommer, 1989; Sommer et al., 1991b)	Elevation is a strong risk factor
Age* (See Figs 4.15 & 4.16) (Tielsch et al., 1991)	Increased risk with increased age
Family History (Perkins, 1974; Becker et al., 1960; Drance et al., 1981)	First degree relatives estimated 4 – 8x more likely to develop POAG
Race (See Figs 4.15 & 4.16) (Tielsch et al., 1991; Arkell et al., 1987; Congdon et al., 1997)	Increased POAG in Blacks Increased ACG in Orientals
Gender (Rudnicka et al, 2006)	Men 1.37x more likely to develop POAG
Trauma (Kaufman & Tolpin, 1974)	Late onset glaucoma after trauma estimated at 2 – 10%
Diabetes (Klein et a.l, 1994; Dielemans et al., 1996; Mitchell et al., 1997; Tielsch et al., 1995)	Increased POAG + SOAG risk
Arterial Hypertension (Hayreh, 1999)	Increased POAG risk in older patients
Systemic Hypotension (Hayreh et al., 1994; Hayreh et al., 1999)	Increased risk with nocturnal hypotension
Refractive Error (Grodum et al., 2001; Mitchell et al., 1999)	Increased risk of POAG with high myopia Increased ACG with high hyperopia
Vasospasm (Tielsch, 1996; Flammer et al., 1999; Flammer et al., 2001; Logan et al., 2006)	Migraine, Raynaud's Syndrome and Vasospastic Syndrome associated with POAG
Central Corneal Thickness (Henriques et al., 2004; Gordon et al., 2002)	Thinner CCT associated with higher risk of POAG + congenital glaucoma
Genetic Mutations and/or Polymorphisms (Rezaie et al., 2002; Funayama et al., 2004, Aung et al., 2005)	Mutations in Optineurin and Myocilin (TIGR) genes implicated in POAG
Light (Osborne et al., 2006)	Light exposure may increase POAG risk due to increased oxidation and increased ganglion cell apoptosis

Table 4a: Risk factors for development of glaucoma

* Comparing patients in their 40s to those in their 80s, the Baltimore Eye Study found that rates increased in caucasians nearly 2.5-fold, from 0.92% to 2.16%, while that of African-Americans increased more than 10-fold, from 1.23% to 11.26% (Tielsch et al., 1991). The Rotterdam Study found

over a 16-fold increase, from 0.2% among those 55 to 59 years of age to 3.3% among those in their late 80s (Dielemans et al., 1994). Finally, the Blue Mountains Study in Australia found almost a 30-fold increase in POAG, from 0.4% among patients in their 50s to 11.4% among those in their 80s (Mitchell et al., 1996).

Glaucoma is a large, varied group of disorders with diverse clinical and histopathological presentations. It is an optic neuropathy characterised by a specific optic nerve head and visual field damage resulting from a number of different conditions that can affect the eye. Quigley (1993) has defined glaucoma as an optic neuropathy due to a progressive loss of ganglion cells. Glaucoma can ultimately be described as the final common pathway of progressive optic neuropathy with resultant loss of retinal sensitivity.

Glaucoma researchers have thus attempted to identify and characterise the nebulous "other factors", to examine a variety of potential mechanisms for disc injury and to search for modes of therapy to better protect the optic nerve. As vision scientists probe its molecular basis, and epidemiologists analyse its existence, clinicians continue to struggle in the management of the condition in the absence of an acceptable and defined means of consistent and effective diagnosis and treatment.

The classic diagnostic triad consists of characteristic nerve fibre bundle defects of the visual field, cupping and associated changes in optic disc structure, and elevated IOP. When these signs are all present, then the diagnosis of glaucoma and the need for treatment are not questioned, but if the diagnostic triad is incomplete, there is no consensus regarding diagnosis and clinical management (nor can there be, given the shortfalls of current testing techniques). Confusion about a definition arises because glaucoma has become nearly a generic vernacular term as for example, stroke or heart

attack. The word has disparate and sometimes even contradictory meanings in different contexts (e.g. slow asymptomatic loss in POAG and sudden painful loss in ACG).

Because we can characterise the glaucomatous optic nerve damage clinically, it is sometimes convenient to limit the diagnosis to patients with optic neuropathy. This thinking requires that a condition in which a patient has elevated IOP but normal discs is designated something different, namely ocular hypertension. It also requires that patients with "possible" neuropathy in the absence of detectable visual field loss be termed glaucoma suspects. Thus, attempts to classify glaucoma solely in terms of the optic nerve or intraocular pressure are flawed. The idea that a variety of pathophysiological factors, including intraocular pressure, play a role in the development of glaucomatous optic neuropathy has become central to our current understanding of the condition.

The glaucomas can be caused by genetic and developmental anomalies or by other previous or concomitant ocular conditions (secondary). In the majority of cases however, no cause for the glaucomatous damage can be found and the glaucoma is termed 'primary open angle' (non-congestive, chronic simple) glaucoma (POAG).

Of all the many different types of glaucoma, POAG occurs by far the most frequently in non-Asians (Fechtner & Kooner, 1997) and is the least well understood. Primary open angle glaucoma can be described as a progressive, bilateral (although often asymmetrical), genetically determined (at least partly, Aung et al., 2005), chronic and slowly progressive optic neuropathy of insidious onset. It is diagnosed as the presence of such neuropathy in the absence of any other cause.

4.4 Classification of Glaucoma

Because the pathophysiology, clinical presentation and treatment of the different types of glaucoma are so varied, there is no single definition that adequately encompasses all forms. It is, like the words cancer and arthritis, an umbrella that shelters a number of decidedly different entities. Understanding this concept helps to explain, for example, why one patient with 'glaucoma' may have no symptoms whilst another experiences sudden pain and vision loss. Glaucoma is therefore broadly categorised, from a diagnostic and pathophysiological perspective, in terms of aqueous fluid drainage into two main types: angle closure glaucoma and open angle glaucoma.

Part of the current study deals specifically with the diagnosis of open angle glaucoma because it is intrinsically more difficult to detect and treat and is therefore the reason for development of a novel preattentive vision test. The following analysis of glaucoma therefore deals principally with this condition although there are numerous areas of overlap that apply to numerous or all forms of glaucoma (see Figure 4.3 and Tables 4b & 4c for an overview of the different types of glaucoma).

Primary Open Angle Glaucomas	**Primary Angle Closure Glaucomas**	**Primary Congenital Glaucomas**
Primary Open Angle Glaucoma	Acute Angle Closure Glaucoma	Primary Congenital Glaucoma
Normal Tension Glaucoma	Chronic Angle Closure Glaucoma	Primary Infantile Glaucoma
Primary Juvenile Glaucoma	Intermittent Angle Closure Glaucoma	Iridocorneodysgenesis

Table 4b: Primary Glaucomas

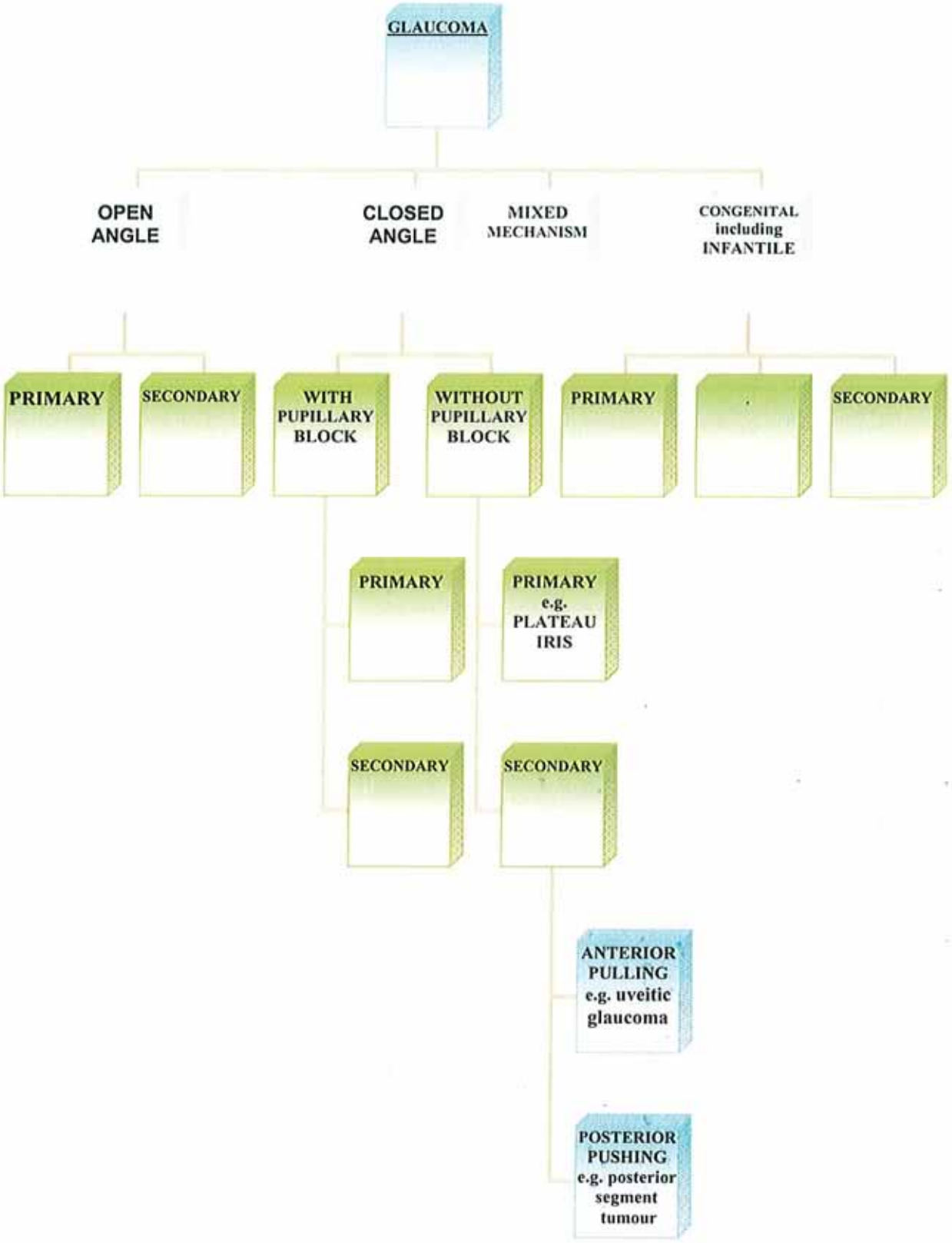


Figure 4.3: Classification of the Glaucomas (modified from :

http://eyelearn.med.utoronto.ca/.../images/02Clas1.gif)

PRETRABECULAR ⇓		TRABECULAR ⇓	POST TRABECULAR
WITH PUPIL BLOCK	**WITHOUT PUPIL BLOCK**	**TRABECULAR OBSTRUCTION/ DAMAGE**	**RAISED EPISCLERAL VENOUS PRESSURE**
Inflammation	Posterior segment disease	Pigmentary glaucoma	Carotico-cavernous fistula
Lens/IOL related	Malignant Glaucoma	Pseudoexfoliation syndrome	Sturge-Weber syndrome
	Small eyes	Lens induced (phacolytic glaucoma)	
	Cellular angle occlusion e.g. rubeosis iridis	Silicone Oil	
	Synechial closure	Haemolytic glaucoma	
		Siderosis	
		Tumour infiltration	
		Uveitic glaucoma	

Table 4c: Secondary glaucomas (modified from: http://eyelearn.med.utoronto.ca/.../images/02Clas1.gif)

4.5 Open Angle Glaucoma

The American Academy of Ophthalmology defines open angle glaucoma as: "Multifactorial optic neuropathy in which there is a characteristic acquired loss of optic nerve fibers", (AAO, 2005).

It can be differentiated from angle closure glaucoma on the basis that the iris is not blocking the trabecular meshwork, which is the primary route of aqueous drainage from the anterior chamber. The drainage angle is thus "open". Some other mechanism is causing the damage to the optic nerve head and nerve fibre layer.

Open angle glaucoma is a broad term that requires further sub-classification into primary open angle (POAG) and secondary open angle (SOAG) glaucoma.

About 70% of the diagnosed cases of glaucoma (in non-Asians) are POAG (Fechtner & Kooner, 1997). The designation of 'primary' indicates that the condition is essentially idiopathic in that there is no known association between the neuropathy and any causative disease process.

In an Irish context, pseudoexfoliation syndrome (PXF) appears to be particularly prevalent (recorded at 1.33% by Coffey et al., 1993, but probably underestimated due to lack of pupil dilation) so that (1) open angle glaucoma prevalence is particularly high (Coffey et al., 1993) and (2) PXF is a common cause of secondary open angle glaucoma here (verbal communication with Prof. C. O'Brien) such that secondary open angle glaucoma may account for a significant percentage of glaucoma cases here.

4.6 Pathophysiology of Optic Nerve Damage

The pathological correlate of glaucoma is the slow death of retinal ganglion cells and their axons that form the optic nerve. The mechanisms underlying such neuronal damage, which include mechanical deformation, vascular insufficiency and neurotoxic injury, have yet to be fully elucidated. These mechanisms are not mutually exclusive and the final common pathway is thought to be ganglion cell apoptosis (Quigley et al., 1995). Glaucoma causes a characteristic pattern of visual field loss. This selective pattern is mirrored in the loss of nerve fibres early in the glaucoma process at the superior and inferior poles of the nerve, where arcuate-area ganglion fibres are located (Quigley & Green, 1979). To understand the mechanism of glaucoma damage it is important to define the site of such damage.

4.7 Lamina Cribrosa Structure

The lamina cribrosa is an area that extends through the optic nerve to cover the posterior scleral foramen. Where the optic nerve passes through the sclera, the latter forms a thin cribriform lamina, the **lamina cribrosa sclerae;** composed of several laminar plates made up of elastin and collagen fibrils. The lamina is characterised by more than two hundred minute orifices, which serve for the transmission of the nerve axons (Radius, 1981a), and the fibrous septa dividing them from one another are continuous with the membranous processes that separate the bundles of nerve fibres. One of these openings, larger than the rest, occupies the centre of the lamina; it transmits the central artery and vein of the retina. Around the entrance of the optic nerve are numerous small apertures for the transmission of the ciliary vessels and nerves, and about midway between this entrance and the corneo-scleral junction are four or five large apertures for the transmission of veins (**venae vorticosae**).

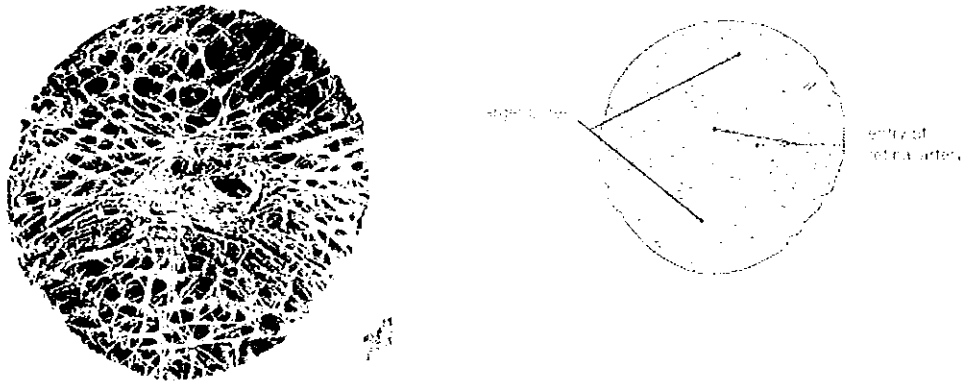


Figure 4.4: Lamina cribrosa structure illustrating pores through which retinal axons pass. The pores have a larger diameter and less supporting collagenous tissue superiorly and inferiorly at the site of characteristic glaucomatous damage. Courtesy: Spalton et al., 2005; p194.

Numerous anatomical studies provide evidence that the optic nerve head is the location of initial cellular insult. Specifically, histological investigations have shown that the axonal fibres are damaged at the lamina cribrosa at the level of the sclera (Gaasterland et al., 1978; Quigley & Addicks, 1981; Quigley et al., 1983). Other investigations have shown that the lamina cribrosa is the site of blockage of axonal transport along the nerve (Quigley & Anderson, 1976; Minckler et al., 1977; Radius, 1981b). Scanning electron microscopy of optic nerve heads also reveals regional differences in the fine structure of the lamina (Quigley & Addicks, 1981). The superior and inferior parts of the lamina contain larger pores and thinner connective tissue support for the passage of nerve fibre bundles than the nasal and temporal parts of the lamina.

Given that the laminar structure appears to be altered (bowed backward) in early glaucoma and also disrupted (retro-displaced) in advanced cases (Quigley et al., 1983), such regional differences may thus explain, at least partly, (ganglion cell size may also

play a role- see section 5.3.2) the characteristic pattern of early glaucomatous field loss.

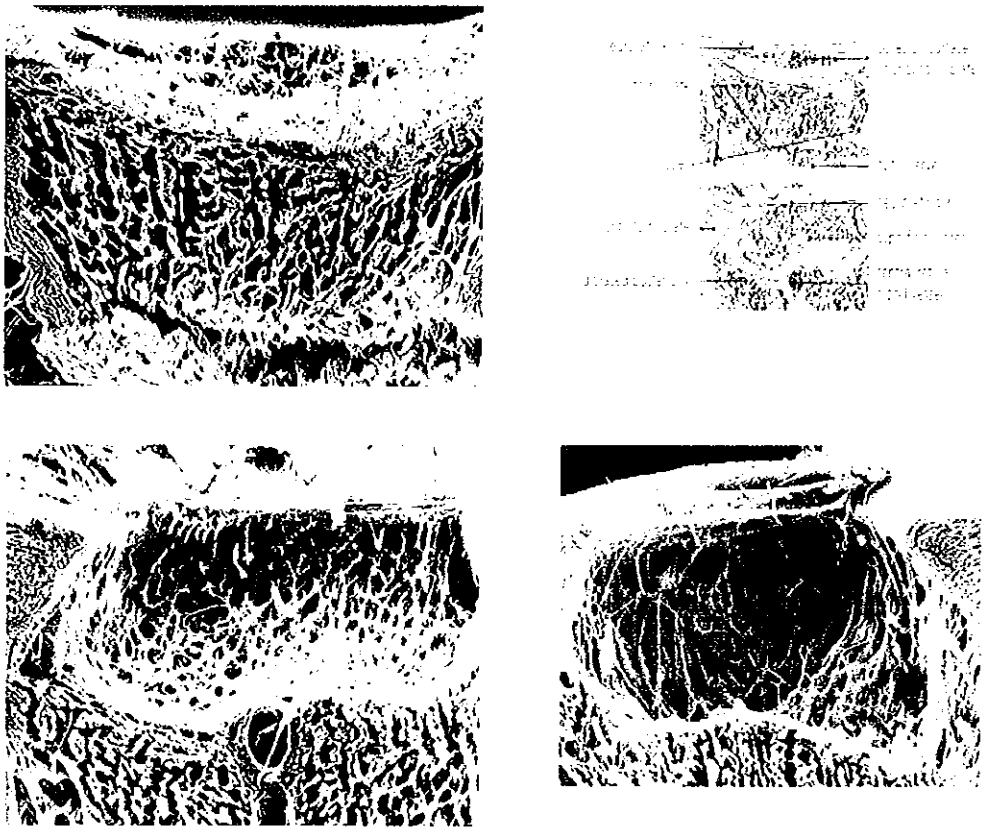


Figure 4.5: Laminar digests illustrating posterior displacement of the lamina cribrosa with glaucomatous damage:

Top left: - normal laminar structure in the absence of glaucoma

Bottom left: - moderately severe glaucoma

Bottom right: - end stage glaucoma Courtesy: Spalton et al., 2005; p194

The above findings seem to indicate that the mechanical compliance of the lamina (i.e. its deformation under a given pressure) plays an important role in glaucoma pathogenesis. Such deformation (posterior bending and lateral distortion) may result from elevated IOP or alternatively from an inherent or acquired weakness in the elastic strength of the lamina.

4.8 Mechanical Theory of Glaucoma Damage

IOP exerts posterior forces on the scleral canal, compressing the laminar plates (Fechtner & Weinreb, 1994). The retrobulbar portion of the optic nerve is covered by meningeal sheaths. These communicate posteriorly with the cerebral ventricular system, and exert a pressure against the lamina cribrosa, which along with intracranial pressure counterbalance the IOP (Hogan et al., 1971).

The mechanical theory is based on observations that the lamina cribrosa is deformed in cases of glaucomatous cupping (Zeimer & Ogura, 1989). Such deformation may result from the loss of the pressure balance either side of the lamina, as a result of a persistent elevation of IOP (altering the hydrostatic pressure gradient) or inherent weakness in the structural integrity of the lamina. Once the critical limit is exceeded the lamina cribrosa deforms, bowing posteriorly and distorting laterally (Levy et al., 1981; Quigley et al., 1983).

The superior and inferior zones of the lamina, having larger pores and thinner supporting sheets of connective tissue are most easily distorted (Quigley et al., 1987; Miller & Quigley, 1988). Early in the process of plate collapse, nerve fibres are lost mostly at these vertical poles of the disc, owing to this lack of support (Quigley & Green, 1979). Increased IOP also results in increased scleral tension that is transmitted to the lamina. This might lead to a change in the shape of the lamina pores, or to an induced misalignment of successive laminar sheets, thus transmitting the increased wall tension to the nerve fibre bundles (Quigley & Addicks, 1981). The lamina cribrosa, because it represents the area of maximum tissue density and also marks the narrowest area along the axon bundle pathway, is the region most prone to compression. Once the laminar plates collapse, the alignment of the axonal channels

distorts, causing the connective tissue structures to impinge on the nerve fibres. Such compression disrupts anterograde and retrograde axoplasmic flow (which is essential to maintain the metabolic machinery of the axon) of the ganglion cell axons, initiating a suicidal response resulting in programmed cell death or apoptosis (Radius & Anderson, 1981; Yablonski & Asamoto, 1993; Quigley et al., 1995).

Yablonski & Asamato (1993) put forward an alternative theory to explain axoplasmic flow blockade. They theorise that there is an inherently unstable condition of axons at the lamina cribrosa. This is because (a) the thin lipid bilayer axolemmal wall of the axon forms a tube that is collapsible, and (b) the axoplasm is a mobile viscoelastic gel that can be forced out of the eye by the steep pressure gradient at the lamina. IOP elevation, they argue, disrupts the supporting structures at the lamina that normally prevent axonal collapse. The result ultimately is axonal collapse and consequent axoplasmic flow blockade. The critical pressure for axonal collapse is critically dependent on 'tube' radius, which explains the predisposition of larger fibres to earlier damage.

The laminar collapse may also alter the microcirculation to the area, affecting axonal metabolism through vascular insufficiency. Astrocytes, which provide physiological and structural support to axons, and maintain the trabecular beams of the lamina may also become dysfunctional, resulting in disrupted axoplasmic transport, direct neurotoxicity (e.g. from nitric oxide), and disruption of the extracellular matrix and cribrosal plate architecture.

Thus, mechanical forces acting on the lamina may result in glaucomatous neuropathy due to direct axonal injury through axonal pinching, or indirect injury through ischaemia, axoplasmic flow interruption and neurotoxicity effects.

4.9 Vasogenic Theory of Glaucoma Damage

The mechanical hypothesis to explain the optic nerve damage of open angle glaucoma has much evidence in its favour. Mechanical forces alone however cannot explain the anatomical and clinical changes seen in glaucoma (Anderson & Hendrickson, 1977). Observations such as the existence of ocular hypertension, 'normal' tension glaucoma, and the finding that glaucoma prevalence increases with age in Japan (Shiose et al., 2001) accompanied by a **decrease** in average IOP are all somewhat at odds with a purely mechanical hypothesis.

It has thus been hypothesised that a reduction in blood flow to the optic nerve head may have a role in the axonal damage seen in glaucoma. Others have taken this further to implicate systemic vascular disease as an important factor in glaucoma pathogenesis, elaborating on Duke-Elder's (1941) assertion that "The point must again be stressed that primary glaucoma is not a local disease of the eyes, but seems more probably the ocular complication of some constitutional disturbance still unknown; nor is the rise of tension the primary pathologic change, for, although it may be the dominant feature, it is merely a symptom of some deeper and more subtle defect. The glaucomatous eye is not merely a hypertonic but a diseased organ, sharing illness with the rest of the body....". Pache & Flammer (2006) have recently compiled a major review of the substantial evidence that a glaucomatous eye is essentially "a sick eye in a sick body", outlining evidence of defects of the cardiovascular, nervous, immune, endocrine and other major systems of the body in association with glaucoma.

4.9.1 Optic Nerve Blood Supply

The ophthalmic artery gives rise to the central retinal artery and two to three posterior ciliary arteries (PCAs) which divide into two long and multiple short PCAs. The short PCA's pierce the sclera adjacent to the optic nerve, anastomoses from which form the circle of Zinn-Haller within the sclera around the ONH, which, along with pial branches of peripapillary choroidal vessels, supply the laminar region of the optic nerve. The prelaminar region is supplied by the large vessels of the peripapillary choroid, and the retrolaminar nerve by pial branches of the peripapillary choroid.

Evidence supporting the vasogenic theory has come from laser Doppler flowmetry evaluations of circulation at the optic nerve (Riva et al., 1992). Studies have highlighted diminished blood flow in the optic nerves of eyes with POAG (Kaiser et al., 1997; Grunwald et al., 1998). Similarly, optic nerve blood flow has been shown to be affected by systemic blood pressure. Subjects with low systemic blood pressure exhibited reduced blood flow while those with systemic hypertension had increased flow (Grunwald et al., 1999).

Other techniques such as colour Doppler imaging, scanning laser Doppler flowmetry, and Doppler optical coherence tomography may also provide useful information on optic nerve perfusion.

A vascular mechanism may have several components relating to (a) systemic and local vascular disease/damage, (b) perfusion pressures at the optic nerve head and (c) autoregulation failure.

(a) Vascular Disease

Drance (1975) emphasised the importance of haemodynamic crises and systemic small blood vessel abnormalities in the production of visual field loss in glaucoma. Thus, low systemic blood pressure, obstructive disease of the large vessels of the neck, intermittent cardiac arrhythmias which reduce cardiac output through intermittent haemodynamic circulatory changes, diabetes with its associated arteriolar disease, and small vessel disease from systemic hypertension are all important factors in the perfusion of the optic nerve head. Bengtsson (1981) is also emphatic in his assertion that systemic vascular problems and not IOP are the prime factors in glaucoma.

The probable effect of such systemic disease is vascular insufficiency at the optic nerve head leading directly to neuronal damage through ischaemia and hypoxia.

Vascular anomalies such as splinter haemorrhages at the disc are often seen in cases of glaucoma, particularly "normal tension" glaucoma. Drance (1989) has suggested that most cases of glaucomatous damage are accompanied by transient disc haemorrhages (even if these are not always observed at infrequent check ups) and reports an expected latency of eight years between the occurrence of a disc haemorrhage and detectable field loss. He therefore suggests that the presence of a disc haemorrhage should be regarded as an indication of early damage in the absence of other possible causes. Such haemorrhages may also occur secondary to atherosclerosis or deformation of vessels around the lamina cribrosa causing direct mechanical damage to optic nerve supporting capillaries.

Leibovitch et al. (2005) suggest that persons with "normal tension" glaucoma may have higher than normal levels of C-reactive protein, an acute phase reactant that is an

important biomarker for atherosclerosis and coronary heart disease. They compared C-reactive protein levels between 20 patients with normal tension glaucoma (NTG) and 30 individuals without ocular disease of comparable age and gender mix. The NTG patients had a statistically significant higher level of C-reactive protein. The researchers speculate that normal tension glaucoma may have a vascular or atherosclerotic aetiology, and they point out the association between elevated C-reactive protein and sleep apnea, which has a high prevalence in patients with normal tension glaucoma (Marcus et al., 2001).

Drance et al. (1988) also report increased incidence of vasospastic disease in POAG patients, especially NTG. Conditions such as migraine and Raynaud's disease and reduced baseline blood flow within the ophthalmic artery have been implicated. A vasospastic response to cold was detected in 65% of NTG patients versus 26% of controls. In patients with normal tension glaucoma (NTG), vasospasm or inappropriate vasoconstriction may cause critical hypoperfusion leading to death of retinal ganglion cells and consequent loss of visual field. Flammer et al. (1999 & 2001) also describe the role of vasospastic disease in the pathogenesis of glaucoma. Such vascular dysregulation interferes with autoregulation and renders the eye more sensitive to IOP increase and blood pressure decrease.

A Belfast study by Logan et al. (2006) has also identified a link between NOS3, one of the isoforms of the enzyme nitric oxide synthase (NOS) and glaucoma patients with migraine headaches.

Morphological and dynamic perfusion alterations have been identified in both "normal tension" and primary open-angle glaucoma (Spaeth, 1975). Fluorescein filling defects of the optic nerve head are areas of non-perfusion and have been described in

glaucomatous optic neuropathy (Schwartz, 1994; Plange et al., 2004). The number, extent and topography of the fluorescein filling defects correspond to visual field loss, and a relationship between nerve fibre defects, cupping and filling defects was confirmed in glaucoma (Piccolino et al., 1985; Plange et al., 2004). Longitudinal studies in glaucoma and ocular hypertension have also confirmed an association between filling defects and progression of nerve damage (Talusan et al., 1980; Tuulonen et al., 1987). Plange et al. (2004) conclude that the extent of these filling defects correlates to visual field loss and morphological damage and therefore suggest that fluorescein angiography may be useful in the diagnosis and management of glaucoma.

Focal arteriolar narrowing of peripapillary retinal vessels, generalised thinning of blood vessels and the presence of venous collaterals all provide further evidence of vascular abnormalities in glaucoma.

(b) Perfusion Pressures

The vasculature of the optic nerve head includes (i) short posterior ciliary arterial supply to the lamina cribrosa and prelaminar region, (ii) choroidal arterial supply of the pre-laminar area and (iii) central retinal arterial supply of the retinal layers. Novack et al., (1990) have shown that IOP directly influences blood flow through the pre-laminar optic nerve. It has also been observed that when IOP is raised above systolic blood pressure, perfusion of the pre-laminar nerve was halted (Sperber & Bill, 1989).

Hayreh (1976) postulates that an increase in IOP reduces perfusion of the prelaminar nerve by altering the normal balance between IOP and blood pressure in the posterior ciliary and choroidal vessels. The concept of 'perfusion pressure' (mean BP minus

IOP) is important in describing the potential effect of either raised IOP or lowered BP. The Baltimore Eye Survey (Tielsch et al., 1995) suggests a strong correlation between low diastolic perfusion pressure of systemic hypotension and POAG (see Figure 4.6 below). Among older patients in particular, a lower perfusion pressure was associated with an increased prevalence of POAG, suggesting a relationship between POAG and ocular blood flow. The authors point out, that patients with a low *diastolic* perfusion pressure had a higher prevalence of POAG although a lower systolic perfusion pressure was also associated with POAG.

Hayreh (1999) also points to the importance of nocturnal hypotension (resulting from reduced sympathetic activity with decreased catecholamines – decreased heart rate, cardiac output and peripheral resistance, causing a 10% average dip in BP in normal individuals) in glaucoma. Glaucoma patients appear to have larger decreases in nocturnal BP, which potentially contributes to the progression of their neuropathy.

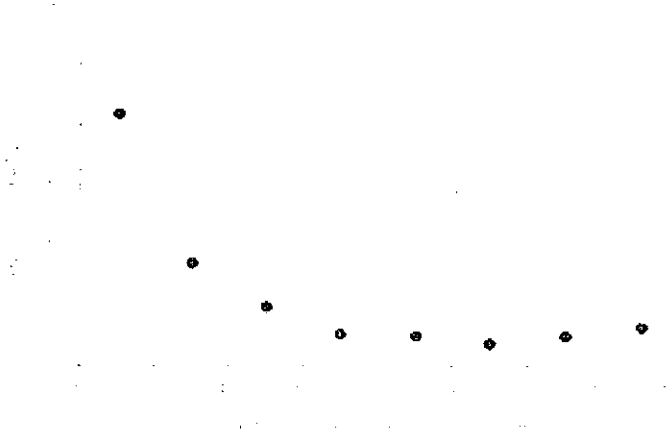


Figure 4.6: Systolic and diastolic blood pressures were collected in patients with POAG as part of the Baltimore Eye Survey (Tielsch et al., 1995). Perfusion pressure was defined as (blood pressure - IOP).

Quigley et al. (2001) studied the effect of diastolic perfusion pressure (which is the diastolic blood pressure - IOP) in Hispanic subjects. Diastolic perfusion pressure was plotted against the percentage of subjects with OAG. The prevalence increased four-fold at a lower perfusion pressure. The percentage of patients with OAG increased steeply as the diastolic perfusion pressure dipped below about 60 mm Hg.

Grunwald et al. (1999) used laser Doppler flowmetry to study the effect of systemic hypertension in 24 eyes of 24 patients with POAG (11of whom had systemic hypertension, 13 did not). All patients were evaluated using laser Doppler flowmetry in three areas of the ONH:

- centre of the cup
- superotemporal rim
- inferotemporal rim

Blood flow, velocity and volume were the main outcome measures. Overall, the average blood flow in the ONH was 29% less in POAG patients compared with controls. The average flow in patients *without* systemic hypertension was 26% less than those *with* systemic hypertension. Mean flow and mean blood pressure were correlated. The authors suggest that a higher blood pressure may result in a higher perfusion pressure, a benefit in maintaining blood flow. They recommend that hypertensive patients treated with an antihypertensive medication may need to be monitored to avoid hypotension in general and nocturnal hypotension in particular because their ONH structures may be more vulnerable to glaucoma.

Ciancaglini et al., (2001) drew similar conclusions in their study of 94 patients with POAG whom they studied with a scanning laser Doppler flowmeter and 30-2 static visual fields. Similar to the Grunwald study (Grunwald et al., 1999), glaucoma patients

had blood flow data that were significantly lower than age-matched, healthy controls both within the lamina and the rim. By comparison, visual field losses of the glaucoma patients were only correlated with blood flow reductions within the lamina cribrosa and not the rim. The authors suggest that decreased blood flow within the lamina may be secondary to connective tissue changes and vascular remodelling within the optic nerve. Graham & Drance (1999) point out the importance of nocturnal hypotension in their report that those glaucoma patients identified as "dippers" had more progressive visual field loss than those without.

(c) Autoregulation

The optic nerve, similar to the rest of the central nervous system, exhibits autoregulation of blood flow (Ulrich et al., 1986). Autoregulation is a physiological phenomenon and means that resistance to blood flow will change dynamically so that flow is constant even as IOP and systemic blood pressure change throughout the day. The chemistry behind autoregulation depends on the release of vasoactive substances in response to vascular smooth muscle stretch (in response to flow changes) and sheer stress of the blood against the endothelial surface.

In a normal eye, autoregulation works well. As a function of age, disease, or both, the capacity of autoregulation may be exceeded or the mechanism itself may become defective. If the IOP of a patient's eye remains high, the venous pressure would necessarily rise to be just slightly higher than IOP to permit venous drainage. When venous pressure rises, perfusion pressure falls and in theory there is not enough blood to flow through the optic nerve vascular bed - even if its vessels were maximally dilated via autoregulation. Alternatively, if the mechanism of autoregulation were intrinsically damaged, then blood flow may be inadequate even at a modest IOP. From

this perspective, lowering IOP medically or surgically will reduce vascular resistance and increase the vascular perfusion pressure.

In an eye with glaucomatous optic neuropathy, it is possible that autoregulation has failed and that the ONH consequently receives repeated vascular insults. Autoregulatory mechanisms have thus been implicated in axonal destruction in glaucoma (Ulrich et al., 1986). It is hypothesised that the normal autoregulation of the optic nerve microvasculature works at a maximum but, for unknown reasons, fails to compensate adequately during periods of retinal stimulation (Sperber & Bill, 1989). Reduction in blood flow in microvascular conditions such as diabetes and systemic hypertension may also interfere with autoregulation resulting in tissue compromise. Retinal blood flow is autoregulated in normals up to a 41% increase in BP. Macular capillary flow is autoregulated up to an IOP of 30mmHg in normals but only to 24mmHg in POAG eyes (Grunwald, 1998).

It is most probable that neither the mechanical nor the vasogenic theories can exclusively describe the ultimate mechanism of cell death. A combined mechanism appears to be more likely. Mechanical compression leads to laminar distortion, resulting in loss of both axoplasm and blood flow. Blood flow may be further reduced by systemic vascular disease. Axoplasmic flow cessation leads directly to cell death, while blood flow disruption leads to ischaemia and interferes with autoregulatory mechanisms. Thus, a compromised lamina cribrosa and a disrupted blood supply both contribute to the progression of glaucoma.

4.10 Excitotoxicity Theory of Glaucoma Damage

Recently the focus has shifted more to understanding the response of nerve tissue to trauma and aging. Data emerging from studies of the central nervous system have led

to the application of new concepts of neurotoxicity and apoptosis to understanding the damage that occurs in glaucoma.

When nervous tissue is severely injured, regardless of cause, it follows the same common final pathway before neuronal death. The injurious events may relate to ischaemia/hypoxia, trauma, hypoglycaemia, stroke and various acute or chronic degenerative and hereditary neuronal processes (Schumer & Podos, 1994). The functional damage to the nervous tissue continues to progress even after the primary cause has been removed.

Astrocytes are abundant in the optic nerve where they communicate with neighbouring astrocytes, Müller cells, and other glial cells within the retina. In the case of an ischemic insult, the nutritional supply to a focal area would be interrupted and this event could be communicated to many retinal astrocytes. A ripple effect could cause a phenomenon known as 'spreading depression' with accompanying voltage changes and increased glucose consumption. An end result may be a release of glutamate, prostaglandins, and nitric oxide that would injure both the retinal ganglion cells and the microglia within the lamina (Osborne et al., 2001). Retinal ganglion cell death may also be mediated by loss of neurotrophic growth factors such as brain-derived neurotrophic factor (BDNF) following cellular insult (Levin, 1999).

The biochemical events surrounding the area of nerve injury involve the release of the excitatory amino acids glutamate and aspartate. These amino acids have the ability to excessively stimulate the nerve and cause neuronal fatigue, toxicity and ultimately nerve death (Olney, 1986). Although glutamate is known to be an important neurotransmitter in the retina, its cytotoxic effects are well known (Lucus &

Newhouse, 1957; Otori et al., 1998). Dreyer et al. (1996) found significantly higher levels of glutamate in the vitreous samples of glaucoma patients compared to normal individuals. Similarly, Brooks et al. (1997) found significantly higher vitreal glutamate concentration in dogs with primary glaucoma compared to normal animals. Even relatively minor but chronic elevation of glutamate may be toxic to the retinal ganglion cells. Both mechanical insult and ischemic insults are postulated to lead to an increase in such excitatory amino acid levels (Olney, 1986). After the release of glutamate at the injury site, sodium ions enter the cell. There is concomitant entry of chloride ions and water, which causes cellular swelling. These events constitute the acute phase of neuronal trauma. Depending on the severity of the insult, the cell may recover or proceed to further loss of function and death. In the second or delayed phase there is cellular influx of calcium and, once the calcium homeostasis is altered, a wide variety of abnormal biochemical reactions ensue. There is release of cytotoxic enzymes such as protease, endonuclease and lipase that destroy the cell membrane. Free radicals accumulate and further disturb the essential metabolic functions of the cells. Glutamate toxicity also releases G protein via its stimulation of metallotrophic receptors, which in turn activates phospholipase C. The end result is major disruption of normal cellular function (Vorwerk et al., 1996).

The term secondary degeneration describes progressive neuropathy that spreads to adjacent areas beyond the initially injured neuron site. The aim of therapeutic neuroprotection is to protect these initially spared neurons from secondary degeneration. The future of glaucoma treatment may include such neuroprotective measures.

Given that there is evidence that up to 50% of retinal nerve fibres may be lost prior to initiation of glaucoma therapy (Quigley et al., 1981; Quigley et al., 1982), these findings have obvious repercussions for the ultimate prognosis in glaucoma. They also help explain why some glaucoma patients continue to show progressive neuropathy even after 'successful' therapeutic intervention.

4.10.1 Apoptosis

Another important pathway for cellular death is apoptosis or programmed cell death (Quigley et al., 1995; Kerrigan et al., 1997). This active process is different from necrosis and, when triggered by calcium, ion imbalance enables the cell to die without liberating its digestive enzymes. Apoptosis appears to be genetically controlled, and because its time-course is longer than that of necrosis, it may be artificially altered in the future to prevent the initiation or advance of the deadly program (Nickells & Zack, 1996; Tatton, 1999). Quigley et al. (1995) have shown that ganglion cell death in glaucoma shares certain similarities with classic apoptosis. Retinal cells in glaucomatous neuropathy display chromatin condensation, involution or shrinkage and formation of apoptotic bodies.

Neufeld et al. (1997) have demonstrated increased levels of nitric oxide synthase (NOS) isoforms 1, 2 and 3 in the optic nerve head of patients with POAG. NOS normally functions to help regulate blood flow. Dysregulation of NOS can theoretically lead to blood flow abnormalities but can also induce neural damage by initiation of an excitotoxic apoptotic cascade. The presence of NOS-1 and NOS-2 suggests that nitric oxide may reach toxic levels in the optic nerve in glaucoma.

Excitotoxicity, even when mild, can cause neuronal apoptosis (Bonfoco et al., 1995). Excitotoxicity of retinal ganglion cells is mediated by overstimulation of a subtype of glutamate receptor, N-methyl-D-aspartate (NMDA). Dreyer et al. (1995) have shown that agents that interfere with translation or transcription of these proteins are also effective in preventing NMDA-induced excitotoxicity. Overstimulation of NMDA receptors activates NOS, which mediates increased levels of nitric oxide and superoxide anion.

In experimental rodent models, blocking NOS has been shown to be effective in decreasing the rate of optic nerve damage without affecting intraocular pressure (Hare et al., 2001).

Given the link between NOS-3 and glaucoma patients with migraine, such patients may be the first to directly benefit from the ongoing research on NOS blocking agents in experimental animals.

The newest theories of glaucoma damage include a combination of all the above possible mechanisms. The initial phase involves the causative mechanism, mechanical insult or vascular deprivation and may be triggered in susceptible patients by factors such as elevated IOP. In the subsequent stages, damaged ganglion cell axons are influenced by neurotropin deprivation and/or the released excitatory amino acids. With the loss of neurotropic support, slow death is inevitable. Consensus exists that these events are interconnected and once initiated are difficult to control with current therapies for glaucoma.

4.10.2 Neuroprotection

Neuroprotection is a very active area of glaucoma research. Glutamate excitotoxicity is suspected to play an important role in glaucomatous optic nerve damage, and

glutamate transporter activity has been found to be decreased in experimental models of glaucoma (Martin et al., 2002). A number of direct and indirect pharmacological approaches to neuroprotection have been explored (Levin, 1999). A direct strategy would involve introducing neurotrophic factors, DNA-encoding these factors, or free-radical scavengers into the eye. An indirect approach would involve activating the intrinsic survival mechanisms of ganglion cells and surrounding glial cells. The aim is to alter the balance between the cell death signals and survival signals (Figure 4.7).

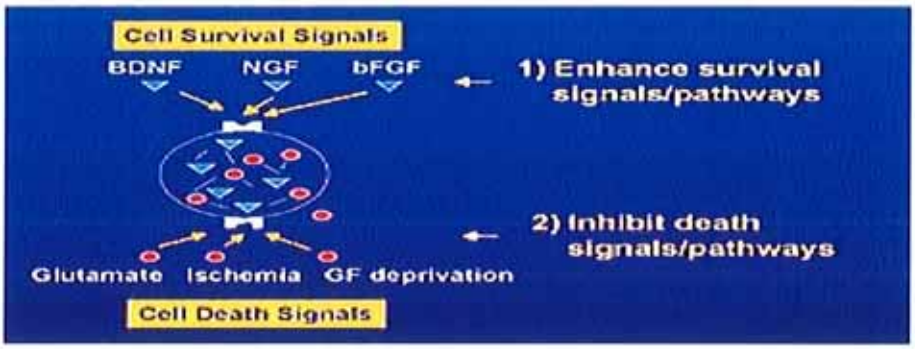


Figure 4.7: Neuroprotection may be achieved by enhancement of survival signals by stimulating/introducing neurotrophins or by inhibiting death signals. From: www.revoptom.com/.../ feb02/glaucoma.htm

Rothstein et al. (2005) found that antibiotics belonging to the beta-lactam class are among the most potent neuroprotective agents currently available. Using rat spinal cord cultures to assay for increased glutamate transporter GLT1 (EAAT2) activity, neuroscience researchers screened more than 1,000 bioactive compounds, including 750 that already have FDA approval for human use. Glutamate transporters deactivate glutamate within the neuronal synapse and prevent toxicity from excess glutamate. Penicillin, amoxicillin, ceftriaxone, and other beta-lactam antibiotics were among the most potent compounds in the assay. In addition, ceftriaxone therapy induced a significant, dose-dependent increase in glutamate transport activity in normal rat brain and spinal cord. Ceftriaxone also slowed loss of nerve and muscle strength in a mouse

model of amyotrophic lateral sclerosis, a neurodegenerative disease that involves glutamate excitotoxicity. Brimonidine (Figure 4.8) and NMDA channel blockers such as Memantine, have shown the most potential as neuroprotective agents (Hare et al., 2001), achieving pharmacologically active concentrations in the retina, and enhancing ganglion cell survival in animal models of optic neuropathy.

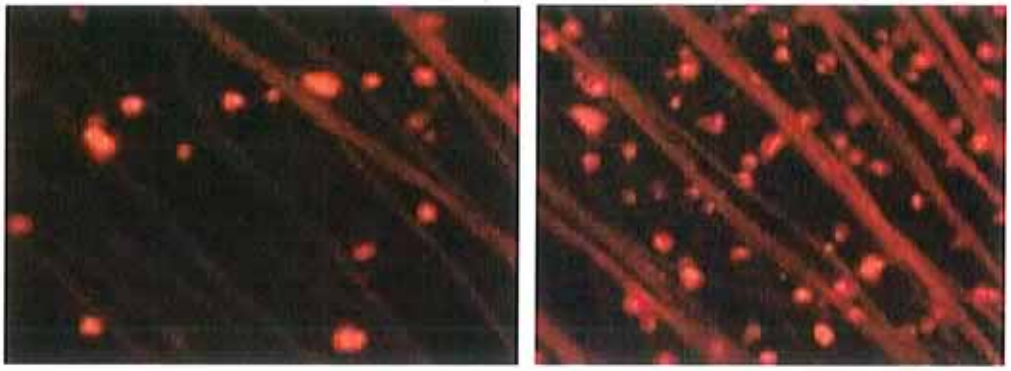


Figure 4.8: In one of the experimental models for retinal ganglion cell injury, the optic nerve crush model, brimonidine exerts a neuroprotective effect as seen by the greater number of fluorescent cells in the retina of animals treated with brimonidine (right panel) compared to vehicle alone (left panel). From: www.revoptom.com/.../ feb02/glaucoma.htm.

Other results suggest that it may be possible to use and augment the body's own defence mechanisms to achieve neuroprotection through vaccination. Schori at al (2001) have shown that immunisation with Cop-1, a synthetic peptide cross-reactive with myelin antigen, significantly reduced ganglion cell loss following direct biochemical insult by glutamate in the rat ocular hypertension model.

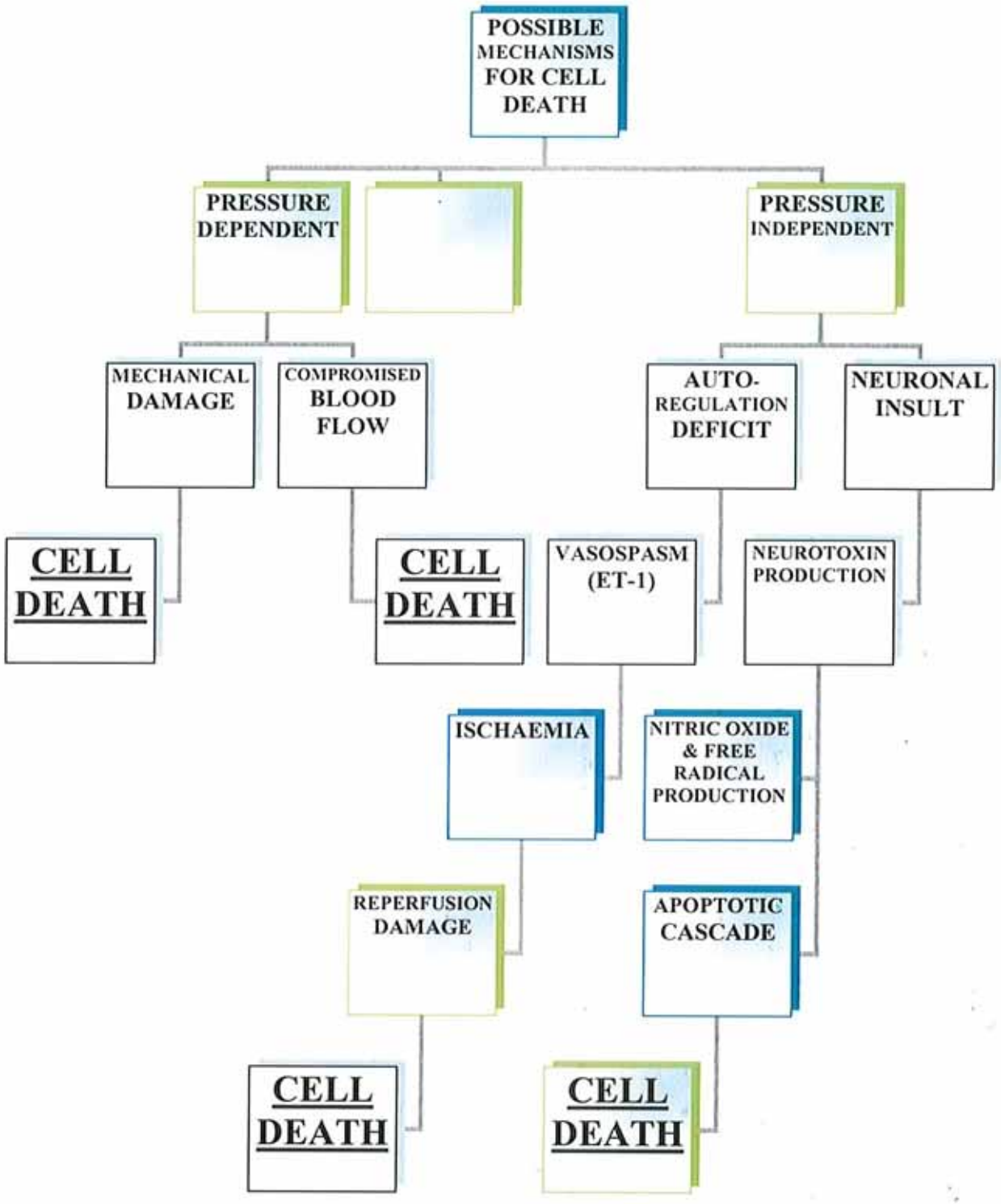


Figure 4.9: Summary of possible mechanisms for cell death in glaucoma.

Figure 4.9 above summarises suggested mechanisms for cell death in glaucoma. The events appear in isolation but there is likely some degree of interconnectivity between the various mechanisms.

4.11 Current Glaucoma Testing Techniques

There are 3 principal techniques that have become the standard in glaucoma detection and analysis of treatment efficacy.

1: Optic Nerve Head & Retinal Nerve Fibre Layer Examination

2: Visual Field Analysis using Automated Perimetry

3: Tonometry.

As Open Angle Glaucoma is an optic neuropathy, characterised by specific optic nerve head and visual field damage, and because increased intraocular pressure is considered an important risk factor, these are techniques of obvious worth. They are valued techniques, but it must be noted that there are severe limitations associated with them, which restrict the ability to detect early glaucoma.

Once structural or functional loss (or both) characteristic of glaucoma is suspected, examination of the anterior chamber is essential to permit differential diagnosis of the glaucomas. A diagnosis of POAG is necessarily one of exclusion and gonioscopic evaluation of the anterior chamber angle anatomy is an essential tool in the diagnosis and subsequent management of the glaucomas.

4.12 Optic Nerve Head and Retinal Nerve Fibre Layer Examination

It has been shown that structural changes of the optic nerve head and retinal nerve fibre layer (RNFL) ganglion cell loss in particular, can be detected several years before visual field defects become manifest (Hoyt, 1972; Quigley et al., 1982; Sommer et al., 1991). Observation of the optic nerve head and RNFL is the single most significant test in establishing the diagnosis of glaucoma (Litwak, 1990; Varma et al., 1993).

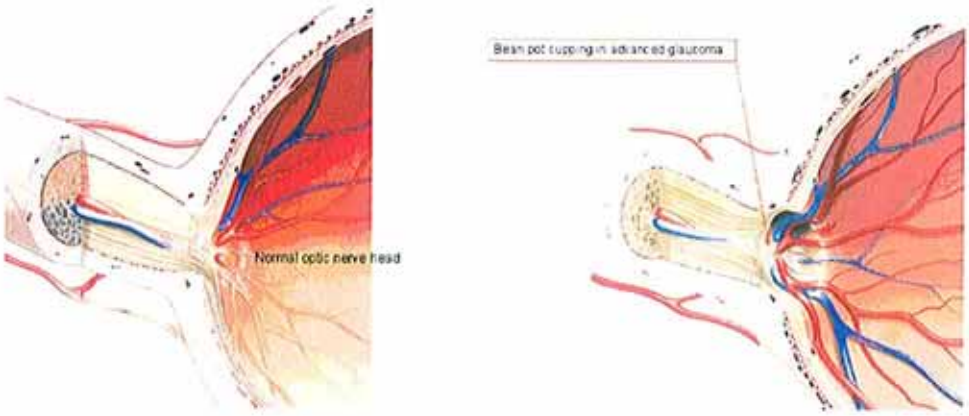


Figure 4.10: Normal optic nerve head and glaucomatous excavation of the optic nerve head. From: www.merckmedicus.com/.../ images/glaucoma08.jpg

Observations such as neuroretinal rim shape (rim thinning and loss of Jonas ISNT configuration) and integrity (focal notching), optic disc size, cup disc ratio, amount of disc cupping, disc haemorrhages, acquired disc pits, baring of circumlinear vessels, peripapillary atrophy, disc pallor and focal or diffuse retinal nerve fibre defects all give an indication as to the presence of glaucomatous atrophy. Particular attention should be given to the detection of ONH/RNFL inter-eye asymmetry and changes in parameters over time to facilitate more confident diagnosis of glaucoma. It is vital however to identify and differentiate non-glaucomatous disc 'abnormalities' such as congenital disc pits, disc colobomas, tilted discs, and changes associated with age and high refractive errors.

The sensitivity of ONH/RNFL examination in glaucoma detection is significantly affected by numerous factors. Tests have demonstrated a large degree of interobserver variability even among 'experts' (Tielsch et al., 1988; Sturmer et al., 1992; Abrams et al., 1994; Gaasterland et al., 2001). There is also a significant degree of overlap of structural measurements between glaucoma and normal patients (Figure 4.11), such that a diagnosis of glaucomatous neuropathy based on ophthalmoscopic findings is often problematic.

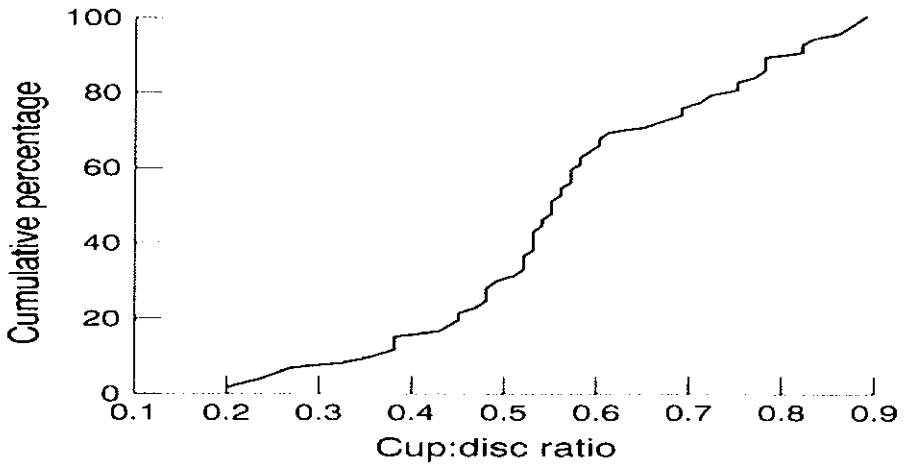


Figure 4.11: The cumulative percentage of vertical CDR distribution among subjects able to complete visual field testing in a population survey in whom a reproducible visual field defect (glaucoma hemifield test "outside normal limits" and a four point cluster (p<5%) on the pattern deviation plot) was identified. (Note 30% C/D < 0.5, which could easily lead to such patients being assessed as normal). (Foster et al., 2002).

Therefore, even with more sophisticated techniques like scanning laser polarimetry, optical coherence tomography or scanning laser ophthalmoscopy, the diagnosis of glaucoma remains quite difficult.

4.13 Visual Field Analysis using Automated Perimetry

Visual field analysis is currently considered an important factor in the diagnosis and management of POAG. It gives a positive indication of functional vision loss associated with nerve fibre losses in glaucoma. In the absence of functional loss it can be difficult to determine if or when to initiate therapeutic intervention. Once a stable and repeatable glaucomatous field defect has been established, perimetry is potentially a very sensitive indicator of progressive functional loss and is therefore the gold standard in glaucoma management.

There are two steps in diagnosing glaucomatous visual field loss using automated perimetry. The first is to determine whether the visual field is normal or not. If the visual field is abnormal, the second step (which is the easier of the two, as determining 'normality' is not always straightforward) is to determine whether the abnormality is due to glaucoma or to something else.

4.13.1 Characteristics of Glaucomatous Field Loss

Glaucomatous field loss is the result of axonal damage at the level of the disc, and is therefore the functional correlate of neural loss or reduced neural function. Most glaucomatous visual field defects are of the nerve fibre bundle type, with damage to ganglion cell axons at the optic nerve head resulting in loss of the nerve fibre bundles. Fibres from the superior and inferior retinas respect the horizontal raphe and given that ganglion cell damage characteristically occurs at the vertical poles of the disc (Quigley & Green, 1979), early losses characteristically affect the superotemporal or inferotemporal bundles first and typically present as isolated paracentral scotomas, nasal steps and arcuate scotomas.

A diagnosis of an abnormal field due to glaucoma is usually made of the basis of a number of clinically viable analytical techniques. Analysis of the pattern deviation plot to identify clusters of abnormal points is a useful technique. Katz et al. (1991) suggest that three contiguous abnormal points that respect the horizontal meridian, at least one of which at the $p < 1\%$ level are indicative of abnormality. Focal abnormalities are similarly identified using the pattern standard deviation indices. The field is considered abnormal if the probability value is less than 5%. The Glaucoma Hemifield Test (GHT) provides an additional diagnostic tool, utilizing the known altitudinal nature of early glaucomatous loss to detect glaucoma on the basis of differences in sensitivity

above and below the horizontal midline (Duggan et al., 1985). If any one of the above criteria is present on a repeatable field test, the visual field is considered abnormal.

4.13.2 Perimetry Shortcomings

It has been shown that structural changes of the optic nerve head and retinal nerve fibre layer (RNFL) ganglion cell loss can be detected several years before visual field defects become manifest (Figure 4.12 - Sommer et al., 1991; Hoyt & Newman, 1972; Quigley, Addicks & Green, 1982; Tuulonen et al., 1993).

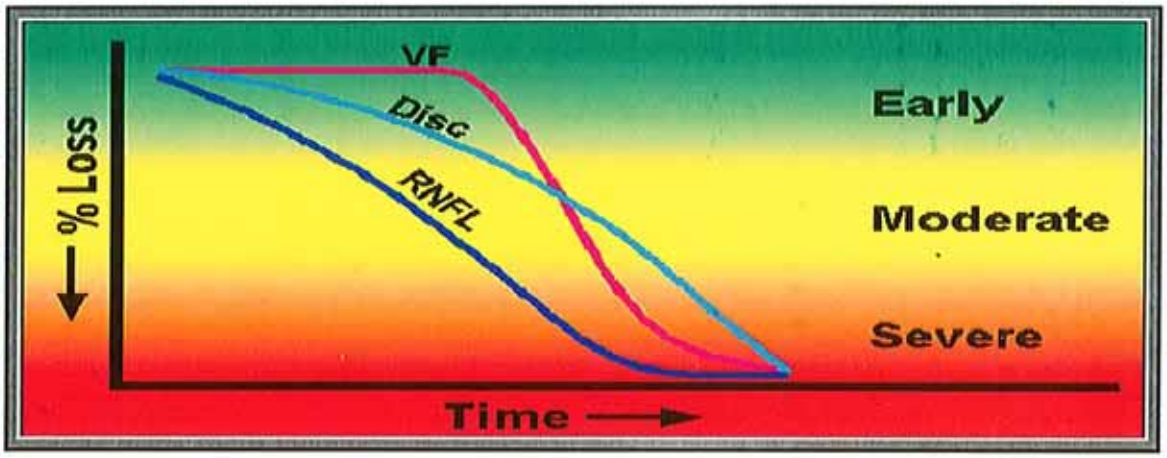


Figure 4.12: Illustration of relative timeframe for detectable losses in glaucoma. Optic nerve and retinal nerve fibre layer abnormalities are generally observable years prior to functional visual field losses. Courtesy: Fannin Healthcare, Ireland (OCT & GDx Presentation).

The redundancy of the visual system provides one explanation why many patients who have early POAG perform the test adequately and defects are not detected until this redundancy has been overcome. One of a number of promising alternatives to conventional perimetry is short wavelength automated perimetry (SWAP). Johnson et al. (1993a), Sample et al. (1993) and Polo et al. (2002) have all demonstrated visual field defects using Short Wavelength Automated Perimetry (SWAP), several years

before the same patients developed defects on standard achromatic perimetry (see detailed description of SWAP in chapter 5).

Quigley et al. (1982) analysed enucleated eyes from normal patients and from those who had been considered glaucoma suspect, but not under treatment, and found that up to 50% of nerve fibres can be destroyed by POAG before defects are found.

Therefore, a normal field result does not necessarily mean the patient is free from glaucomatous nerve fibre damage. The observation that those patients with more advanced glaucoma at the initial diagnosis have increased risk of progression (Tezel et al., 2001), and require maintenance at lower IOP values to slow progression (Grant & Burke, 1982), highlights the importance of making a diagnosis at the earliest possible stage in the process.

For these reasons vision scientists have sought to develop functional tests that are more sensitive to the earliest functional losses of glaucoma in order to minimise the visual loss suffered by the patient and potentially improve the patients' prognosis. For a detailed analysis of such developments see Chapter 5.

4.14 Tonometry

The historical link between IOP and glaucoma has been covered previously in section 4.2. Observations such as progressive nerve loss in the presence of elevated IOP, sudden nerve loss in the acute rise of IOP in angle closure, mechanical deformation of the optic nerve in the sustained presence of elevated IOP, glaucomatous damage in experimentally induced IOP elevation in animals (Quigley & Addicks, 1980) and

successful management of glaucoma by IOP reduction techniques (Kass et al., 2002) have all helped establish a link between IOP and glaucoma.

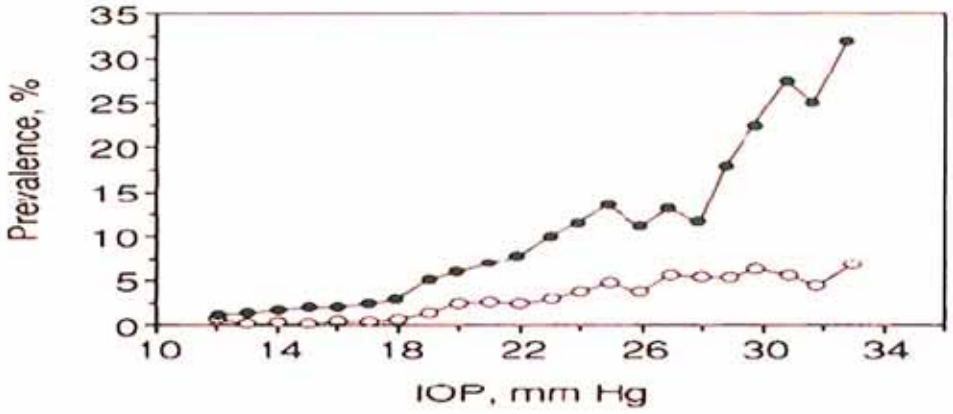


Figure 4.13: Prevalence of POAG in relation to screening IOP among African American subjects (closed circles, n=4,674 eyes) and Caucasian American subjects (open circles, n= 5,700 eyes). Sommer et al. (1991a)

Elevated IOP measurements should therefore be treated as a significant risk factor and as an essential management tool for glaucoma. However, as previously outlined, there are numerous objections to the use of tonometry in the diagnosis of glaucoma. Principally, the variation in IOP among glaucoma patients (Figure 4.13), the presence of conditions such as ocular hypertension and normal-tension glaucoma and the significant degree of overlap in IOP measurements between patients with and without glaucoma (Figure 4.14), indicate that, while the risk of damage may be dependent on the level of IOP (Anderson & Hendrickson, 1977; Sommer, 1989), there is no fixed IOP at which the presence of glaucoma can be determined, since damage can occur at any level.

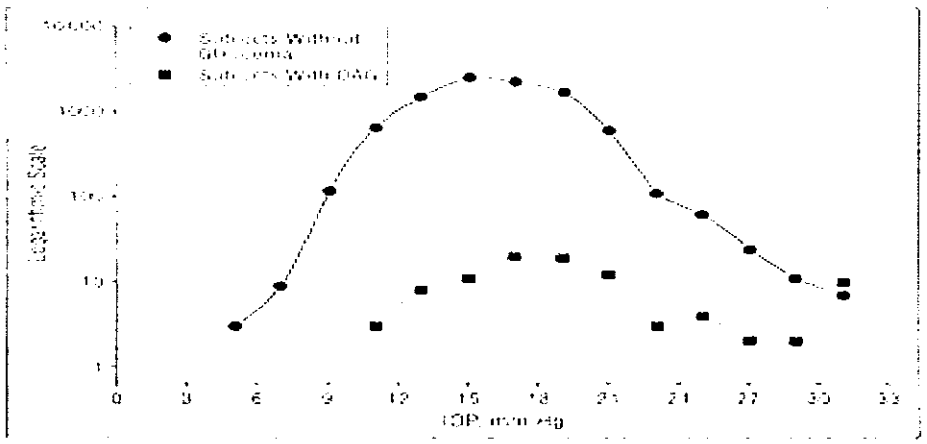


Figure 4.14: Distribution of IOP among normal and glaucoma patients. While the mean is higher for the glaucoma patients, the distribution patterns are similar. Only at 31mmHg is the prevalence of glaucoma higher than normalcy. Quigley et al., 2001.

The concept of normative pressure should therefore emphasize that it is not the statistically normal, but the individually normal IOP that is important. Since there is no known means to determine the individually normal IOP, the diagnostic capabilities of tonometry have to be seen as quite limited. Other factors such as diurnal and seasonal IOP variations (Shiose, 1990), effect of with-the-rule (underestimation of IOP) and against-the-rule (overestimation of IOP) corneal astigmatism (Holladay et al., 1983), and the effect of corneal thickness (Damji et al., 2003) and corneal hysteresis also limit the accuracy of tonometry in establishing the "true" IOP, again compromising the diagnostic ability of the test.

Tonometry therefore, should be utilised to determine the level of risk of glaucoma development and not to attempt to determine "normalcy". It does not give sufficient data to either indicate the presence of glaucoma or, more importantly, to exclude it. Factors that contribute to variability in IOP such as the effects of age (Hollows and Graham, 1966; Shiose, 1984a; Coffey et al., 1993), race, sex, diurnal (Bengtsson,

1972; Kitazawa & Horie, 1979), seasonal (Blumenthal et al., 1970; Bengtsson, 1972; Shiose, 1984b) and postural (Leonard et al., 1983; Anderson & Grant, 1973) variations, and corneal thickness and rigidity (Ehlers et al., 1975; Brandt et al., 2001; Gordon et al., 2002) mean that attempts to establish a "normal" IOP are essentially futile. All patients should be examined with equal vigour for glaucoma, using all available tests regardless of the IOP measurement.

4.15 Epidemiology of Glaucoma

Knowledge of the epidemiology of POAG is an essential step if we are to more fully understand this enigmatic neuropathy. Epidemiological studies are concerned not only with the manner in which the condition arises and is distributed in the population but also with attempts to identify, using population based studies and comparisons, those factors genetic and environmental which might account for the pattern of distribution that is observed. Such knowledge can serve to (i) resolve controversy regarding definitions of glaucoma, (ii) to allow more accurate diagnosis of those suffering from early glaucoma and (iii) to identify those most likely to develop glaucoma.

The absence of a universally accepted definition of POAG has posed significant difficulties for epidemiological studies. An appropriate case definition is the keystone of epidemiological research. Analysis of existing glaucoma prevalence data from a number of studies across diverse populations highlights the difficulties associated with glaucoma in that most studies use different definitions to identify a case of glaucoma, using different IOP, optic nerve and visual field threshold criteria. This makes it difficult to compare the results of different studies with confidence.

Traditionally, glaucoma has been categorised not by mechanisms of damage to the optic nerve but by the mechanisms that cause an elevation of IOP, namely primary or secondary open or closed angle glaucoma. Understanding the differences between the traditional and the newer terminology of glaucoma is essential to placing the epidemiological and socioeconomic data about glaucoma in the proper context.

In a break with the traditional categorisation of the glaucomas, the new American Academy of Ophthalmology (AAO, 2005) definition of primary open-angle glaucoma states that the disease is multifactorial in origin but that it primarily affects the optic nerve. IOP is an important element of the group of putative causes of damage to the optic nerve, but it is not the only one. As such, the new definition (including that of the European Glaucoma Society) of POAG has no IOP criterion. It requires only optic nerve damage that is consistent with the clinical syndrome to be present for a diagnosis of glaucoma to be made. Furthermore, by definition, early glaucoma has no associated visual field loss. Instead, the presence of any characteristic glaucomatous field loss automatically makes the glaucoma of at least moderate severity.

Based on current definitions and deficiencies in diagnostic techniques, it can be assumed that most prevalence studies underestimate (possibly quite significantly) the number of persons with glaucoma. Thus, the major focus today is not on the drainage pathways of the eye but on injury to the optic nerve and how best to prevent or even reverse such injury. The definitions and terminology used in glaucoma most likely will change over the next few years. Despite this problem however, existing studies tend to show similar patterns of prevalence.

4.15.1 Glaucoma Prevalence

Studies have shown that glaucoma is the second leading cause of blindness in the United States (Leske, 1983) as well as the second leading cause of bilateral blindness in the world, second only to cataract (Quigley, 1996). Friedman et al. (2004) estimate the prevalence of open angle glaucoma to be 1.86% for adults 40 years old and above. Kelliher et al. (2006) report glaucoma to be the second leading cause of registered blindness in Ireland, accounting for 12% of all blind registrations in 2003 (although the actual prevalence may actually be significantly higher; the same authors found that 21% of patients' eligible for blind registration had not been so registered). Quigley (1996) estimates that 66.8 million people worldwide would have glaucoma by the start of the twenty first century (1.02% of the world's total population or 4.12% of the world's population > 45 years of age (*World Population Prospects: The 2004 Revision*, 2005).

Open and closed angle glaucoma are estimated to be of almost equal prevalence, primarily because of the high prevalence of angle closure in the Chinese population (1.73%) compared to OAG (0.58%) – see Table 4d below. All non-Asian populations exhibit increased incidence of OAG relative to ACG. Data relating to secondary glaucoma is difficult to assess as most studies fail to make a proper distinction between primary open angle glaucoma and the secondary glaucomas. There is also a paucity of information pertaining to the prevalence of congenital and infantile glaucoma. Coffey et al. (1983) cite anecdotal evidence of increased prevalence of glaucoma in Ireland and report a prevalence of 2.39% among those over the age of fifty in the West of Ireland. This breaks down into 1.88% POAG (~50% NTG), 0.09% ACG, 0.41% Secondary OAG. A further 1.05% were classed as suspects and 3.61% as ocular hypertensives.

Group	OAG	ACG	Total Population	OAG: ACG Ratio	OAG Prevalence (%)	ACG Prevalence (%)
China	7,444,663	22,333,990	1,288,704,314	0.33	0.58	1.73
India	5,591,042	5,591,042	1,435,699,181	1.00	0.39	0.39
South Asia	4,224,819	4,224,819	769,979,570	1.00	0.55	0.55
European derivation	6,945,870	609,287	1,116,845,880	11.4	0.62	0.06
Africa	7,026,081	46,285	723,834,244	151.8	0.97	0.01
Latin America	1,278,751	560,856	506,533,880	2.28	0.25	0.11
Near East	640,040	280,719	323,624,981	2.28	0.20	0.09
Total	33,151,266	33,646,997	6,165,222,154	0.98	0.54	0.55

Table 4d: Estimated number of people with glaucoma (Quigley, 1996)

Rochtchina & Mitchell (2000) also estimate that the prevalence of glaucoma in Australia will increase from current estimates of between 144,000 persons (Blue Mountains Study, Mitchell et al., 1996) and 167,000 (Melbourne Visual impairment Project, Wensor et al., 1998) to between 307,000 and 337,000 persons respectively by 2030. Table 4e gives an overview of the major glaucoma prevalence studies.

Study Site	Population Minimum Age	Overall Rate (%)	Youngest Group (%)	Oldest Group (%)	ACG Rate (%)	2^0 Glaucoma Rate
Beaver Dam (Klein et al, 1992)	≥ 43	2.1	0.9	4.7	0.04	
Baltimore (Tielsch et al., 1991)	≥ 40	4.2 Black 1.3 White	1.23 Black 0.92 White (40-49)	11.26 Black 2.16 White (80+)	0.9 Black 0.4 White	
Framingham (Leibowitz et al., 1980)	≥ 52	1.4	0.5 (55-59)	4.4 (80-84)		
Blue Mountains, Australia (Mitchell et al., 1996)	≥ 49	3	0.4 (49-59)	11.4 (80+)		
Rotterdam (Dielemans et al., 1994)	≥ 55	1.1	0.2 (55-59)	3.3 (85-89)		
Barbados (Leske et al., 1994)	≥ 40	7.0 Black 3.3 Mixed 0.8 White	1.4 (40-49)	23.2 (80-86)		
St. Lucia (Mason et al, 1989)	≥ 30	8.8				
Melbourne (Wensor et al., 1998)	≥ 40	1.7	0.1 (40-49)	9.7 (80-89)	0.1	0.2
Egna- Newmarkt, Italy (Bonomi et al., 1998)	≥ 40	2			0.6	
Ponza, Italy (Cedrone et al., 1997)	≥ 40	2.51			0.97	0.29
Mongolia (Foster et al., 1996)	≥ 40	0.5		6.4		
Roscommon, Ireland (Coffey et al., 1993)	≥ 50	2.39	0.72	3.05	0.09	0.41
Ferndale, Wales (Hollows & Graham, 1966)	40 - 74	0.84	0.06	2.49	0.09	0.26
Dalby, Sweden (Bengtsson, 1981)	55 - 70	1.25	0.7	1.8	0.1	0.27

Table 4e: Overview of published studies on the prevalence of glaucoma

Glaucoma prevalence is seen to increase exponentially with age. Among African and Asian derived persons, the relationship between prevalence and age is a linear one,

with Africans having the highest prevalence (four to five times higher) of open angle glaucoma in all age groups (Figures 4.15 & 4.16).

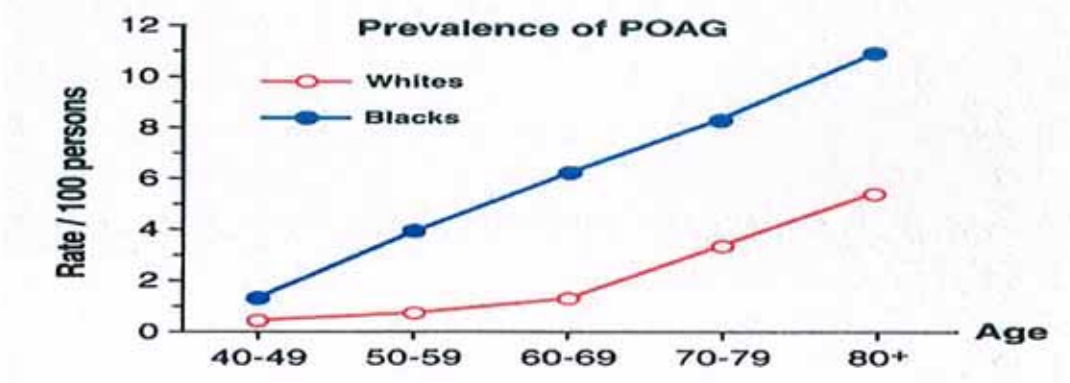


Figure 4.15: Age-prevalence relationship of open angle glaucoma among African Americans and Whites from the Baltimore Eye Survey (Tielsch et al., 1991). POAG exhibits earlier onset and is more prevalent among every age group over 40 among those of African decent. Whether this is due to race or factors such as the larger optic nerve heads and thinner central corneal thicknesses associated with black patients has been questioned (Zangwill et al., 2004).

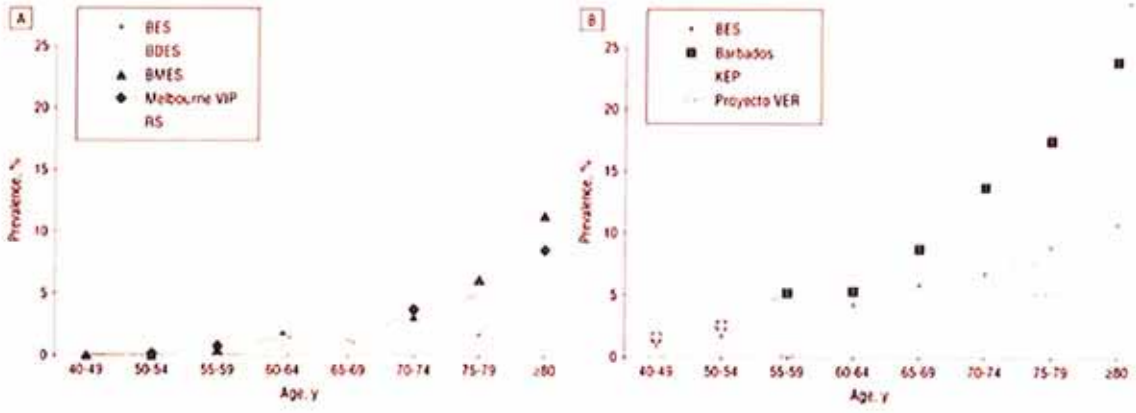


Figure 4.16: Prevalence of glaucoma in white (A) and black and Hispanic (B) subjects from various prevalence studies above illustrating the effect of age and race. (BES= Baltimore, BDES = Beaver Dam, BMES = Blue Mountains, RS = Rotterdam, KEP = Kyoto)

The most salient features from all these prevalence studies are:

- Normal IOP in 30-50% of glaucoma cases
- Applying new definitions (e.g. early glaucoma does not need a field defect to establish a diagnosis) to existing data would increase prevalence rates (e.g. Beaver Dam prevalence would increase 31%, Barbados would increase 55%). It is probably safe to assume an underestimation of at least one-third.
- Age appears to be probably the most significant factor in glaucoma prevalence. Among all populations, prevalence increases significantly with advancing age. In fact, age is possibly a more sensitive indicator of risk than IOP except at very high IOP's.
- Racial variations should influence diagnostic and therapeutic strategies (e.g. initial treatment may need to be more aggressive in patients of African descent).
- Most studies report an existing diagnosis of glaucoma in only 50% of those evaluated. The other 50% remain blissfully unaware of the presence of this progressive neuropathy.
- The advent of newer diagnostic techniques may also result in higher prevalence rates.

Thus it can be seen that currently available prevalence estimates cannot be judged with a high level of confidence to be truly representative of the extent of glaucoma within certain subpopulations or the opulation at large. These epidemiological studies however have highlighted the fundamental flaws associated with current diagnostic techniques and outlined future research needs to identify all risk factors and causative mechanisms for glaucoma, and to develop more sensitive diagnostic techniques and apply a universal set of diagnostic criteria.

CHAPTER 5

NOVEL TECHNIQUES FOR GLAUCOMA DETECTION

5.1 Introduction

Traditionally, to have a diagnosis of glaucoma, you had to have a patient with high IOP, cupping and visual field defects. Now we know that there are glaucoma patients with normal IOP, we also see glaucoma without cupping, cupping without glaucoma, and glaucoma without visual field defects. Exploration of synergies in glaucoma diagnosis brought the recognition that glaucoma encompasses a spectrum of disorders and the realisation that no single test can provide a reliable differentiation between glaucoma and normals in all cases.

Epidemiological studies consistently reveal that approximately 50% of people with glaucoma are as yet undiagnosed (see section 4.15). Given the aforementioned limitations of existing glaucoma screening strategies, the above figure of 50% is likely to be a conservative estimate. The established link between visual prognosis and extent of damage at the time of diagnosis (Wilson et al., 1982; Tezel et al., 2001), and the recognised limitations of conventional diagnostic techniques (see Chapter 4) have provided the rationale for development of more sensitive tests of both visual function and optic nerve/retinal nerve fibre layer structure.

Recent studies have shown that glaucoma accounts for 12% (representing a marginal increase since 1996) of all blind registrations in Ireland (Kelliher et al., 2006). Studies in Scotland and Israel have confirmed a similar blindness rate of 14% due to glaucoma (Bamashmus et al., 2003; Farber, 2003). Many of these people could avoid significant vision loss if their glaucoma were diagnosed and treated in the earliest stages.

Recent advances are easing the burden of clinical diagnosis in glaucoma. Breakthroughs in technology, lessons learnt from clinical studies and improved

normative databases are setting a new standard of patient care. New glaucoma detection devices simplify the screening strategy, are often more patient and practitioner friendly and facilitate easier differentiation between normals and glaucoma.

5.2 Structural Tests of ONH & RNFL Integrity

There remains some debate still as to whether structural or functional losses are the earliest detectable effects of glaucomatous neuropathy. Currently, structural defects of the ONH and RNFL are the earliest detectable losses. Novel tests of structural integrity offer the benefits of more objective analysis of the ONH and RNFL, direct indications of glaucoma status and most importantly, the ability to provide longitudinal analysis for detection of change

5.2.1 Scanning Laser Polarimetry

Scanning laser polarimetry (SLP) is concerned exclusively with determination of the thickness of the retinal nerve fibre layer. Recognition of defects of the RNFL potentially provides the earliest indication of glaucomatous loss (Figure 4.12). SLP compares the measured RNFL thickness with a robust normative database to ascertain 'normality' based on age-matched, sex-matched and race-matched comparisons. Scanning laser polarimetry (SLP) relies on the birefringent property of the RNFL to provide an indirect measure of RNFL thickness. Such birefringence occurs in structures that consist of a regular arrangement of parallel microtubule fibres. The SLP passes polarised light into the eye. The form–birefringent RNFL splits this ray into orthogonally polarised, phase shifted components (the cornea causes a similar phase shift but this effect is eliminated by variable, individualised corneal compensation).

SLP measures the resultant phase shift (termed retardation). The amount of retardation correlates linearly with the thickness of the RNFL (Weinreb et al., 1990).

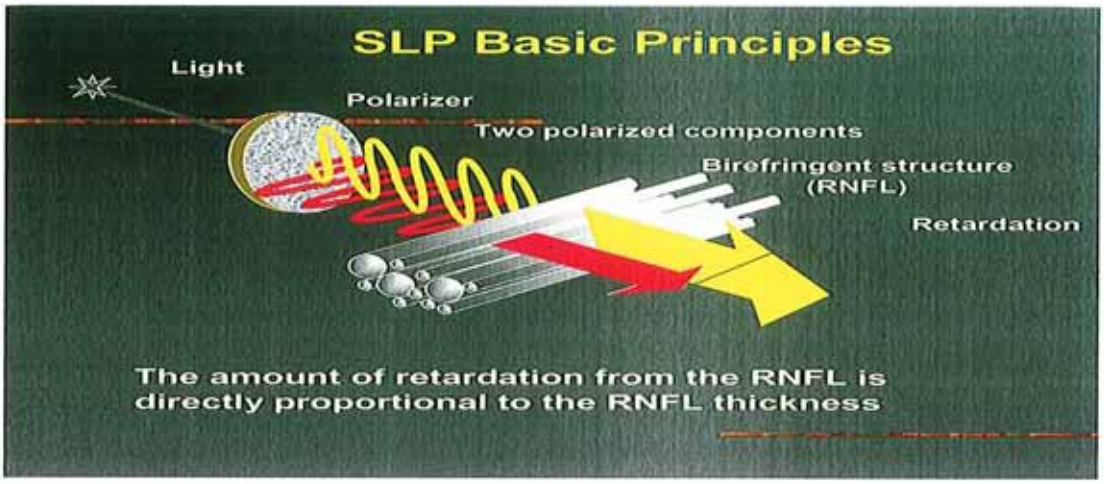


Figure 5.1: Principle of RNFL thickness measurement by SLP based on tissue birefringence. Courtesy: Fannin Healthcare, Ireland (GDx Presentation).

SLP provides numerous graphical and numerical indices to allow the practitioner to determine whether an abnormality of RNFL thickness exists.The software also facilitates longitudinal assessment for detection of change through a serial analysis printout that compares results over time, with any change in parameters from the baseline measurements illustrated graphically.

Numerous studies confirm that SLP in the form of the GDx VCC (variable corneal compensation) accurately differentiates normals from glaucoma patients with high sensitivity and specificity (Weinreb et al., 1998; Trible et al., 1999; Zangwill et al., 1999; Zangwill et al., 2000(b); Zangwill et al., 2001; Greaney et al., 2002; Essock et al., 2003; Reus & Lemij, 2003; Weinreb et al., 2002), and that it detects the presence of RNFL defects prior to visual field loss on standard achromatic and frequency doubling perimetry (Bowd et al., 2001; Horn & Nguyen, 2003), and most significantly, that it is capable of identifying those patients with suspicious discs but normal visual

fields most likely to progress (Choi et al., 2002; Mohammadi et al., 2003(a); Mohammadi et al., 2003)

The principal benefits of SLP include its objectivity (more sensitive than RNFL photography (Medeiros et al., 2003), repeatability, ease of use (patient and practice friendly), and its capacity for early glaucoma detection. It is limited by the fact that it is concerned almost exclusively with the diagnosis of glaucoma and possibly other optic neuropathies (Homan et al., 2002; Sunaric Megevand et al., 2002). It is an expensive instrument and therefore may be deemed unsuitable for routine clinical practice (perimetry has wider scope of practice for example).

5.2.2 Optical Coherence Tomography

Optical coherence tomography (OCT) is a diagnostic imaging technique that performs high resolution (maximum ~ 3 – 10 microns, which is at least double that of other techniques such as MRI and Ultrasound) tomographic imaging (Drexler et al., 2001) of the internal microstructure of biological tissue by measuring the echo time delay and intensity of backreflected and backscattered light by low-coherence interferometry (Fujimoto, 2003). OCT enables real-time in situ visualisation of retinal tissue with such fine resolution that the principal layers of the retina are definable (Figure 5.3). As such it provides a virtual histological section of the retina without the need for tissue excision required by conventional biopsy techniques (Fujimoto et al., 2000), thereby facilitating diagnosis and guiding intervention in cases of retinal pathology.

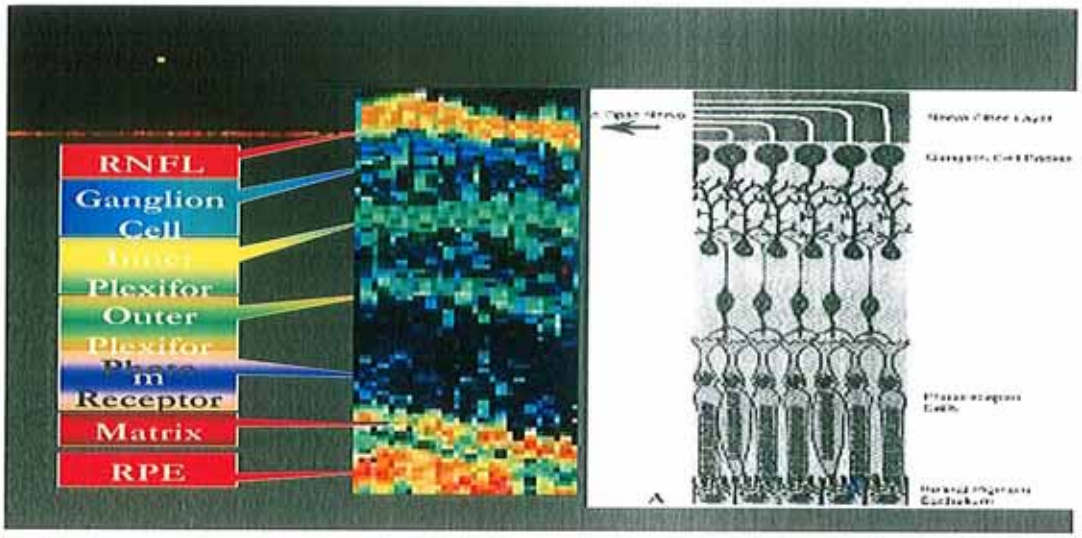


Figure 5.3: Illustration of retinal layers as imaged by optical coherence tomography Courtesy: Fannin Healthcare, Ireland (OCT Presentation).

OCT is possible because light is backreflected from boundaries between different tissues and backscattered differently from tissues that have different optical properties. The position and dimensions of the various tissue layers is determined by measuring the echo time delay of light that is backreflected (light is reflected at interfaces of tissues with different refractive indices) or backscattered (heterogeneous media scatter light due to index variations caused by sub-cellular structures or bundles of smaller structures, e.g. nerve fibre axons) from the different structures at varying axial distances.

5.2.2.1 OCT in Glaucoma

Given the ultrahigh resolution capabilities of the OCT (about 8 – 10 microns better than GDx which has a resolution capacity of 13microns), it is natural to assume that it has enormous potential as a diagnostic tool for the earliest detection of glaucomatous optic nerve damage. Given its unique ability to independently and objectively assess the structural integrity of **both** the optic nerve head and the nerve fibre layer surrounding the nerve head, the OCT is potentially a valuable tool in glaucoma

management. The thickness of the nerve fibre layer which can prove a reliable indicator of early glaucoma for example, can be measured, quantified and correlated with measurements of optic nerve head structure or visual function (Bowd et al., 2000; 2001; Zangwill et al., 2000(a); Schuman et al., 2003). Comparative studies have revealed similarly high sensitivities to early glaucomatous damage for the OCT and the GDx (Medeiros et al., 2004; Leung et al., 2005).

Results are presented and analysed in a variety of ways. Average thickness values are computed and displayed with a colour code indicator of normality (green = normal, yellow = suspect, red = abnormal). The measured thickness values are compared to an age matched normal database values and the RNFL thickness graph is displayed as a function of position around the nerve, with a similar colour code for normative comparison. The results of both eyes are displayed together for symmetry analysis. OCT has consistently proved to be (i) a reliable indicator of established glaucoma (Schuman et al., 1995; Schuman et al., 2003; Guedes et al., 2003; Medeiros et al., 2006) detecting structural defects that correlate with functional damage (Bowd et al., 2001), (ii) capable of detection of the earliest signs of glaucoma damage prior to achromatic visual field loss (Bowd et al., 2000; Reus & Lemij, 2005; Bagga et al., 2006) and (iii) more sensitive than established structural assessment techniques (Zangwill et al., 2000(b))

The principal benefits of OCT include its objectivity, repeatability, ease of use, high resolution and its wide scope of practice for a variety of retinal pathologies (indeed glaucoma would not be a primary indication for OCT). It is somewhat limited though by cost, pupil dilation requirement and is affected by eye movement, dense media opacities and other artefacts.

5.3 Functional Tests of ONH & RNFL Integrity

Traditionally, conventional white on white perimetry provided the clinical gold standard for glaucoma diagnosis and monitoring of treatment efficacy. However it has been well established that such conventional perimetric techniques are unable to detect the earliest losses of visual function. Structural defects are detectable several years prior to field losses, and histological studies have revealed losses of up to 50% of ganglion cells in the absence of any detectable field loss (see section 4.13.4 – perimetry shortcomings). Despite such findings, conventional visual fields remain an important tool in glaucoma detection and management strategies. Only recently have alternative perimetric techniques become clinically viable for early glaucoma detection.

5.3.1 Early Functional Losses in Glaucoma

Clinically, ganglion cell loss manifests as optic disc cupping and defects in the nerve fibre layer before the onset of visual field changes. The insensitivity of conventional perimetric stimuli most likely reflects the non-selective nature of the achromatic stimuli used, and the significant degree of overlap of ganglion cell receptive fields in all retinal locations i.e. there may be numerous ganglion cells capable of detecting the light stimulus in every retinal location tested, thereby masking early loss until sufficient damage occurs to reveal the underlying defects. It seems unlikely that structural change, which is largely dependent on cell death, precedes cell dysfunction. Therefore, this functional damage if it can be measured should be the first indicator of abnormality in many eyes.

The recent development of novel psychophysical tests for the evaluation of glaucoma is based on several basic strategies that are not necessarily mutually exclusive. Such strategies have been based on the following hypotheses:

- Selective Loss Hypothesis
- Reduced Redundancy Hypothesis
- Population Response Hypothesis

5.3.2 Selective Cell Loss Hypothesis

In recent years a number of studies have suggested that some ganglion cells may have a greater susceptibility to the damaging effects of glaucoma (Quigley, 1987; 1988; Quigley & Green, 1979; Quigley et al., 1982; 1987; 1988; 1989; Glovinsky et al., 1991; 1993). Such studies have suggested that there is a selective loss of large diameter optic nerve fibres throughout all portions of the optic nerve. In particular, such losses occur at the vertical poles of the nerve head (where large diameter axons are most prevalent, and where the earliest damage occurs in glaucoma). Such results have focussed attention on development of tests of magnocellular ganglion cell function. Magno (M) cells are concerned with detection of flicker and movement have correspondingly larger axon diameters for rapid neuronal transmission (De Monasterio, 1978; see section 3.4), and therefore have been purported to be the earliest cells to be affected in glaucoma.

There is much evidence in favour of the selective cell death hypothesis. There are two aspects to such a hypothesis. The first is that glaucomatous cell damage is selective for cell size and second, that it is selective for cell type. The evidence for preferential loss of larger cell axons is strong and persuasive. Large ganglion cells located in the retinal

mid-periphery are selectively damaged in human and experimental glaucoma (Glovinsky et al., 1991). Glovinsky et al. (1993) also report that foveal ganglion cell loss is size dependent (larger cells damaged initially). Glaucoma has also been observed to cause a reduction of axonal flow to the magnocellular layers of the lateral geniculate body subserving the retinal mid-periphery (Dandona et al., 1991). These observations have stimulated considerable interest in psychophysical tests of the magnocellular pathway due to the high prevalence of large diameter axons in this pathway. Knowledge of the characteristics of retinal ganglion cell subgroups (size, distribution, density and function) can be used to guide the design of specific tests for glaucoma. A test that preferentially stimulates a subgroup of ganglion cells with large cell bodies can potentially detect glaucomatous damage earlier, not only because of their presumed greater vulnerability, but also because of their lower density (M-cells account for approximately 10% of the retinal ganglion cell population – Perry et al., 1984; Kaplan et al., 1990; Schiller et al., 1990(a); Merigan & Maunsell, 1993; Kaplan, 2005).

Many recent studies, inspired by histopathologic results, have demonstrated functional losses of the magnocellular pathway. In particular, studies of motion coherence (Silverman et al., 1990), motion displacement thresholds (Fitzke et al., 1987; 1989; Poinoosawmy et al., 1993), flicker and temporal modulation sensitivity (Casson & Johnson, 1993; Casson et al., 1993; Tyler, 1981; Tyler et al., 1992), critical flicker fusion perimetry (Lachenmayr & Drance, 1992; Lachenmayr & Gleissner, 1992), multiflash campimetry (Brussell et al., 1987, Faubert et al., 1987; 1989), peripheral resolution acuity (Anderson & O' Brien, 1997), scotopic sensitivity (Drum et al., 1986), and frequency doubling perimetry (Johnson & Samuels, 1997; Quigley, 1998; Serguhn & Spiegel, 2001; Cello et al., 2000; Horikoshi et al., 2001) have been introduced as a means of evaluating visual functional properties thought to be

mediated by the magnocellular pathway. The vast majority of these studies have detected abnormalities in glaucoma suspects with normal visual fields. This has been interpreted as psychophysical evidence for a selective M-cell loss in glaucoma.

In isolation, this can easily be seen as a logical interpretation. The overall picture however is not so straightforward. There is also mounting psychophysical evidence of early losses of parvocellular functional sensitivity. Tests including pattern discrimination perimetry (Drum et al., 1989a; 1989b; Nutaitis et al., 1992; Chauhan et al., 1993), high-pass resolution perimetry (Frisen, 1989; Airaksinen et al., 1990; Sample et al., 2000; Graham & Drance, 1995), colour discrimination (Sample et al., 1986), and short-wavelength automated perimetry (Sample & Weinreb, 1992; Sample et al., 1986; 1993; Johnson et al., 1993a; 1993b) have all demonstrated the ability to detect early losses of visual function.

Morgan (1994) and Johnson (1994) have also questioned the accuracy of the interpretation of the anatomical/histopathological data and suggest that alternative explanations may be more plausible. Morgan (1994) argues that a decrease in numbers of a particular cell size (larger cells) does not simply translate into selective cell loss of one particular cell class. In particular, the extent of overlap in cell size distribution among all cell classes complicates any attempt to interpret cell size losses as indicators of cell type losses (there are approximately the same number of P-cells as M-cells at the measured mean diameter of 25 microns for M-cells, only for a reducing number of the largest cell sizes do M-cells outnumber P-cells).

Such inconsistencies mean that selective cell type death is no longer widely accepted. Instead, glaucomatous cell death is presumed to be rather non-selective. Currently, the concept of "reduced redundancy" as introduced by Johnson (1994) provides a more useful approach to functional test development.

5.3.3 Reduced Redundancy (Undersampling) Hypothesis

Johnson (1994) introduced the reduced redundancy hypothesis to provide an alternate explanation for the manifestation of early functional losses in glaucoma in the absence of conventional achromatic perimetric defects. As with the selective M-cell loss theory, this hypothesis considers differential losses that are present for specific nerve fibre subpopulations. However it also takes into account the inherent redundancy or sampling properties that are present for a specific nerve fibre subpopulation. Thus, a test that isolates a sparse subpopulation of optic nerve fibres (i.e. one with minimal overlap and redundancy) may reveal early functional losses more readily, even if there are proportionately greater losses for other nerve fibre subpopulations.

The reduced redundancy hypothesis can thus be used to make numerous predictions

- The visual function with the least amount of redundancy should reveal the most extensive and earliest glaucomatous losses (confirmed with SWAP)
- Tests requiring the integrated activity of adjoining regions to perform the task should also be quite sensitive (see Population Response Hypothesis below).
- There should also be a sequential progression of functional losses present in localised regions of the visual field, depending on the relative amount of redundancy for each function evaluated. Longitudinal observations by Casson et al. (1993) of SWAP and temporal-modulation perimetry with standard achromatic perimetry support such basic predictions of the reduced redundancy model.
- Other stimulus attributes that decrease the number of neural elements responding to a particular stimulus (e.g. reductions in stimulus size) should reveal earlier and more extensive glaucomatous losses. Numerous studies have

confirmed the clinical importance of spatial summation in glaucoma (Fellman et al., 1989; Osako et al., 1991; Uyama et al., 1993).

5.3.4 Population Response Hypothesis

Another approach (although basically an extension of the reduced redundancy model) that has proved useful utilises tests that require the combined responses of neighbouring and overlapping receptive fields of optic nerve fibres in order to perform the psychophysical task (e.g. spatial or motion coherence). Such a strategy overcomes the receptive field overlap problem and studies have indeed confirmed that tests of both motion coherence (Silverman et al., 1990) and pattern-discrimination perimetry (Drum et al., 1989a; 1989b; Nutaitis et al., 1992; Chauhan et al., 1993) are more sensitive than standard achromatic perimetry.

5.3.5 Short Wavelength Automated Perimetry (SWAP)

Colour vision disturbances in the different types of glaucoma have been described since 1883 (Pacheco-Cutillas et al., 1999). Early research found red-green colour defects following optic nerve damage from glaucoma. More recent studies however indicate that blue-yellow defects are the most common in glaucoma. Drance et al. (1981) report that such blue-yellow defects can precede nerve fibre damage, although they also note the presence of normal colour vision in some patients with advanced glaucoma. This inconsistency possibly reflects the difficulty in attempting to identify defects through foveal assessment in a condition where foveal sensitivity is characteristically maintained until the final stages.

Historically, it was assumed that the peripheral retina was essentially colour blind. Wooten & Wald (1973) found evidence however that all central colour vision

mechanisms are also present in the periphery albeit at decreasing sensitivities. Noorlander (1983) confirmed that the peripheral retina was sensitive to colour contrast at nasal eccentricities out to 90 degrees. Central to such findings was the employment of large test stimuli in the retinal periphery.

There is anatomical and psychophysical evidence that blue cones are much less prevalent, both at the fovea and in the periphery, than red or green cones. It is estimated that blue cones may account for as little as 2-3% of foveal cones (Walraven, 1974). Gouras & Eggers (1982) also found a relative paucity of blue cones and their neural connections (only 5-10% at the ganglion cell level).

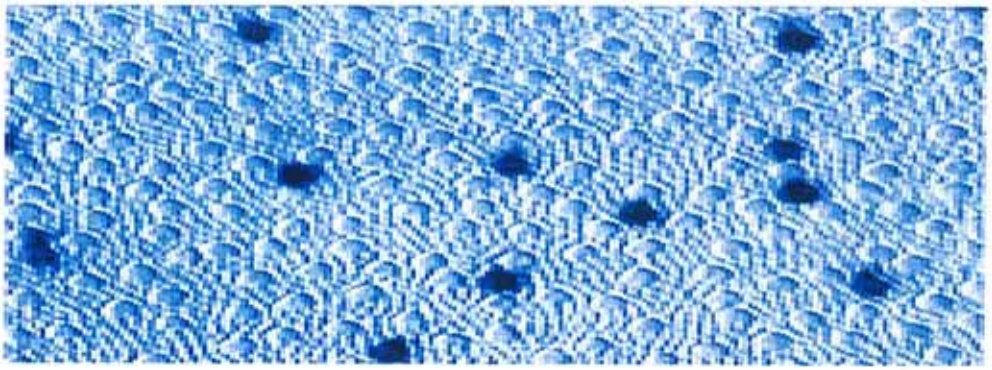


Figure 5.4: Retinal under-sampling of blue cone cells. From:

http://www.univie.ac.at/neuronale-systeme/doc/docGrafik/Cone_mosaic.jpg

Thus, knowledge of (i) the tritan nature of glaucomatous colour loss, (ii) the peripheral nature of glaucomatous field loss, (iii) the sparse, minimally redundant, under-sampled representation of the blue cone system (whose ganglion cells coincidently tend also to have larger diameters than other P-cells) and (iv) the relative insensitivity (Mollon, 1982) of blue cones have all contributed to interest in chromatic perimetric techniques, and in particular, to the development of a test of blue-yellow sensitivity, namely Short Wavelength Automated Perimetry (SWAP).

SWAP employs a large, (Goldmann size V – to account for decreased sensitivity of blue cones in the peripheral retina) blue 440nm stimulus, presented on a high luminance (100 cd/m2) yellow background (to bleach the red and green systems and make them less sensitive to the blue stimulus than the blue cones - Johnson, 2002; Soliman et al., 2002). Extensive prospective and longitudinal investigations of SWAP have revealed that it detects similar but deeper and more extensive visual field losses in patients with existing achromatic glaucomatous field defects, and that it detects losses 3 to 5 years prior to achromatic losses and these are predictive of onset and location of future achromatic losses (Sample & Weinreb, 1992; Johnson et al., 1993a; 1993b; Sample et al., 1993; Bayer & Erb, 2002; Polo et al., 2002).

Given the clearly defined benefits of SWAP over conventional methods, and the commercial availability of SWAP on some of the most commonly used perimeters, the question arises as to why SWAP has not become the gold standard of diagnosis and management? The answer lies in the fact that several limitations exist with regard to this testing strategy.

In particular, the increased test time (10 to 15 minutes per eye) is a significant factor. Bengtsson (2003) has addressed this issue by developing a SITA strategy that can be applied to SWAP. This reduces the test time to as little as 3.6 minutes per eye. It also increases the dynamic range of SWAP (low sensitivity is also a problem for conventional SWAP - (SITA SWAP -21db, Full Threshold SWAP -17.3db). This is not as yet commercially available and needs some work particularly in relation to extending the reference database. Grayscale interpretation is also more difficult given the reduced overall sensitivity and the altitudinal differences observed with superior relative insensitivity sometimes masquerading as a false arcuate defect. The reduced sensitivity also means that SWAP is less useful in cases of advanced glaucoma, so

achromatic perimetry may be better to monitor established glaucoma, and SWAP better to detect earlier losses.

It has also been observed that short term fluctuation (SF) and long term fluctuation (LF) are both larger for SWAP (Kwon et al., 1998; Blumenthal et al., 2000; Spry et al., 2001) causing increased difficulty for result interpretation due to this increased variability within and between tests (possibly due to increased learning effects or increased "noise" effects on a small neuron population). Variability appears to be lower in the faster SITA strategy (Bengtsson, 2003).

Another principal source of difficulty is the increased pre-retinal absorption of short wavelength light by the aging crystalline lens (Said & Weale, 1961). The macular pigment in front of the photoreceptors within the central 5 degrees or so of the retina contains xantophyll, which also selectively absorbs short wavelength light. Variations in the amount of such absorption between patients are difficult to quantify. Given the age profile of glaucoma patients, this remains a significant factor in the interpretation of SWAP results.

5.3.6 Frequency Doubling Perimetry

Numerous investigators have used some form of harmonically pure stimulus to study various properties of human vision. Kelly (1966) thought it logical to determine the interactions between the waveforms used to investigate the spatial and temporal visual systems by sinusoidally modulating the stimulus in both time and space simultaneously. The "surprising" (Kelly reported that the results were unexpected as the deLange and other flicker fusion models could not account for the results) outcome of such a stimulus is the appearance of a spatial second-harmonic response at high flicker rates. For photopic stimuli, if the temporal frequency is greater than about 10Hz

and the spatial frequency is less than 4 cycles per degree (cpd), then the displayed pattern appears to have twice the spatial frequency of the original stimulus (Figure 5.5). Kelly (1981) later interpreted spatial frequency doubling as due to a temporal integrator or low-pass filter that follows suprathreshold non-linearities in the visual pathway. This may correspond to activation of a subclass of magno cells known to respond in a non-linear manner (the M_y-cells). A linear response would result in the fusion of the counter-phase gratings over time into a uniform gray area instead of the frequency doubled appearance.

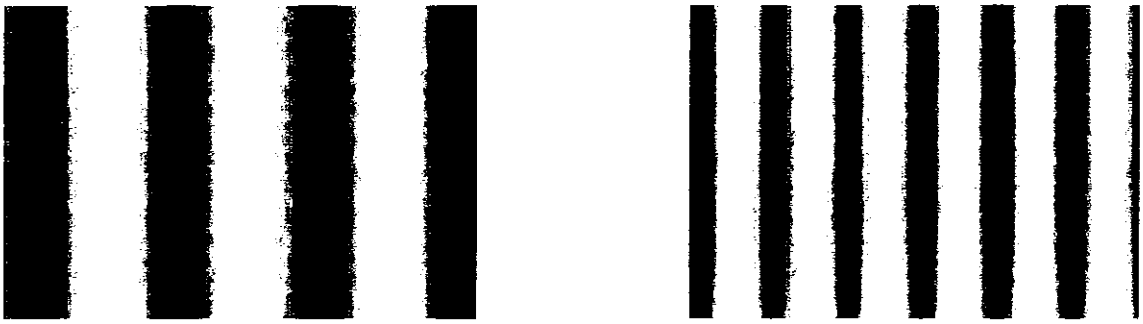


Figure 5.5: Spatial frequency doubling illusion. When the grating on the left (with a spatial frequency between 0.1 – 4 cpd) is alternated in counter-phase (black and white bars alternate with each other) at a relatively rapid rate (>15 Hz), the grating on the right appears with twice the spatial frequency of the original grating. From: www.opt.pacificu.edu/.../13902-GL/Fig12n.jpg

In laboratory experiments recording the responses of single cells in the LGN of the macaque monkey, between 5 to 20% of the cells in the magnocellular layers are found to respond with a nonlinear or Y type of response that is dominated by second harmonic distortion (Kaplan & Shapley, 1982; Marrocco et al., 1982; Derrington & Lennie, 1984; Blakemore & Vital-Durand, 1986). Single cell electrophysiological studies also indicate that M_y cells have larger receptive fields and more rapid

conduction velocities than M_x cells (Kaplan & Shapley, 1982; Marrocco et al., 1982; Blakemore & Vital-Durand, 1986).

Maddess & Henry (1992), because of the assumption of selective loss of large diameter cells in glaucoma, applied the high temporal frequency, low spatial frequency target as a potential screening tool for glaucoma. Interestingly, given the undersampling of such M_y cells (accounting for between 0.5 to 2% of all ganglion cells) the reduced redundancy and population response models of early loss would also suggest that frequency doubling perimetry should be a sensitive indicator of early glaucoma. Frequency doubling therefore has vast potential for the early detection of glaucoma. Numerous investigators have since evaluated and developed frequency doubling technology and it has recently become commercially available as a screening device (Humphrey FDT) and a more comprehensive device for faster full thresholding (uses ZEST (Zippy Estimation of Sequential Thresholds) algorithm – shortens the threshold determination process similar to SITA, Turpin et al., 2002) and complete statistical analysis with more stimuli and more test options (Humphrey Matrix).

5.3.6.1 Frequency Doubling in Glaucoma

The performance of frequency doubling in the detection of glaucoma needs to be evaluated from a number of perspectives. The sensitivity and specificity of the test to established glaucoma, its ability to detect losses in glaucoma suspects without conventional field loss, and its usefulness as a screening device are all of obvious importance. Frequency doubling consistently performs with very high sensitivity and specificity to established glaucoma (typically above 90% on both counts). The majority of prospective studies on the efficacy of frequency doubling have been carried out using the earlier Humphrey FDT. Even with significantly reduced testing

times, frequency doubling perimetry correlates closely with glaucomatous field defects on conventional perimetry even in early cases (Johnson & Samuels, 1997; Johnson et al., 1997; Sponsel et al., 1998; Quigley, 1998; Cello et al., 2000; Osako et al., 2000; Trible et al., 2000; Casson et al., 2001; Serguhn & Spiegel, 2001; Wadood et al., 2002).

There is little evidence as yet however to clarify whether it is capable of detecting pre-perimetric glaucoma losses. The development of the Humphrey Matrix, with its increased capability for full thresholding and statistical analysis may prove more capable that the original FDT of detecting such losses.

The major advantage of frequency doubling appears not to be in the detection of glaucoma earlier than conventional perimetry, but in its potential as a clinically viable screening tool. Both the Humphrey FDT and Humphrey Matrix perform a rapid screening program that takes less than one minute per eye. Even in the screening mode rather than full threshold, sensitivity remains exceptionally high (Trible et al. (2000) report 86% versus 88% sensitivity for screening and threshold strategies respectively in moderate glaucoma; Wadood et al. (2002) report 91.4% sensitivity in screening mode; Quigley (1998) reports 91% sensitivity also in screening mode).

The average test time for frequency doubling technology is significantly faster than alternative techniques. Quigley (1998) reports an average test time of 1.8 +/- 0.7 minutes per eye for the FDT. Wadood et al. (2002), in a comparison of FDT with tendency-oriented perimetry (TOP) and SITA-FAST perimetry (both fast thresholding techniques) found mean test times of 1.08 +/- 0.28 mins (FDT), 2.31 +/- 0.28 mins (TOP) and 4.14 +/- 0.57 mins (SITA FAST). The time differences were statistically

significant. Interestingly, the FDT displayed the highest sensitivity of the three tests. No functional test has shown such potential for viable, large scale glaucoma screening. Screening has therefore largely been confined to tonometry and ONH/RNFL analysis. The high sensitivity and short test time of frequency doubling combined with its resistance to blur, portability and ease of use offer obvious screening merit.

The FDT is limited to a certain extent in that it can miss or obscure neurological defects (including hemianopic defects) that spare the central visual field (Wall et al., 2002). The FDT is also not advocated for sequential threshold testing to monitor glaucoma (Humphrey Matrix is more suited to this). It also only tests the central 30 degrees and so may be of little use in conditions affecting the more peripheral field.

5.4 Alternative Tests

Numerous other structural and functional techniques have been developed as potential indicators of early glaucomatous damage. Those structural techniques receiving most attention include the scanning laser ophthalmoscope (Heidelberg Retinal Tomograph – HRT II) which has shown potential similar to that of both the GDx and the OCT.

Numerous authors have demonstrated early functional losses of colour vision (Drance et al., 1981; Sample et al., 1986; Kalloniatis et al., 1993; Sample et al., 1994; Alvarez et al., 1997), contrast sensitivity (Daubs et al., 1984; Wood & Lovie-Kitchin, 1992) and electrophysiological potentials including pattern electroretinogram (Wanger & Persson, 1987; Ruben et al., 1994) and visually evoked potentials (Motolko et al., 1982) in glaucoma. Table 5a provides a summary of additional alternative functional tests that have received considerable attention, but which are as of yet not widely used or available. The table clearly illustrates significant loss of numerous visual functional

capabilities in the absence of clearly definable field loss on standard achromatic perimetry, and reinforces the concept that a normal achromatic field result does not necessarily indicate normal retinal and nerve function, but may reflect its inability to detect dysfunction.

FUNCTION	OHT	SUSPECT (Mod-Risk)	SUSPECT (High Risk)	CONVERTS TO GLAUCOMA	REFERENCE
Achromatic Perimetry	0%	0%	0%	0%	By definition
SWAP	12%	47% 78%	100%	56% 100%	Johnson et al (1993a) Sample et al (1993) De Jong et al (1990)
High-Pass Resolution Perimetry		58%			Wanger & Persson (1987)
Pattern Discrimination Perimetry	50%				Drum et al (1987)
Temporal Contrast Sensitivity	83%	28%			Drum et al (1989a)
Temporal Modulation Perimetry	36%			60%	Tyler (1994)
Spatial Contrast Sensitivity	63%	35% 30%	50%		Lachenmayr & Drance (1992) Casson et al (1993) Ross et al (1985)
Motion Perception	36%				Silverman et al (1990)

Table 5a: Review of studies illustrating the percentage of OHT and glaucoma-suspect eyes showing abnormalities on alternative psychophysical tests of visual function but normal achromatic conventional fields (cf: SWAP results).

EXPERIMENTAL PROCEDURES, RESULTS & ANALYSIS

CHAPTER 6

EXPERIMENTAL TECHNIQUES

6.1 Introduction

The aims of this project at the outset were twofold. First, the existing pre-attentive visual search (PAVS) software program (written by Dr. Ian Flitcroft) was to be used to determine the effects of numerous visual parameters and also of glaucoma on PAVS efficiency. The second was to enhance the software so as to (a) facilitate the investigation of potentially complicating factors and (b) thus improve the diagnostic capacity of the PAVS test in glaucoma. To this effect, numerous experimental methods have been devised and employed. Such methods shall be covered in the following chapters detailing the findings of the experimental data collection. Numerous software enhancements have been made through additional features and several versions of the program have been developed to achieve (a) and (b) above. The program has thus been treated very much as a work in progress (but remained unchanged during the course of any experimental paradigm). The following is a description of the basic instrumentation, the methodologies employed, the software changes and the rationale behind all strategies and changes adopted.

6.2 Instrumentation

The visual search test was presented on a 19-inch Iiyama colour monitor (Vision Master ^{TM} 450, model S901GT) with 640 x 480 resolution at 80 Hz refresh rate and dot pitch of 0.26 mm. The test area subtended 33.8° horizontally and 25.8° vertically at a fixation distance of 50cm. The white targets and distractors subtended 0.92° with a 1.83° gap between stimuli. Neither targets nor distractors were presented within the blind spot. The software used to present and control the experiment was adapted from that used by Flitcroft et al. (1996); it was written in ANSI C and run on a Pentium 1 PC running at 100MHz.

Targets were white with mean luminance of 132cd/m^2; mean background luminance was 2cd/m^2 giving a Michelson contrast ratio of 0.97. The flicker target was a white filled square box of the above dimensions, square-wave modulated at 16Hz, and surrounded by identical non-flickering boxes as the distractors (Figure 6.1).

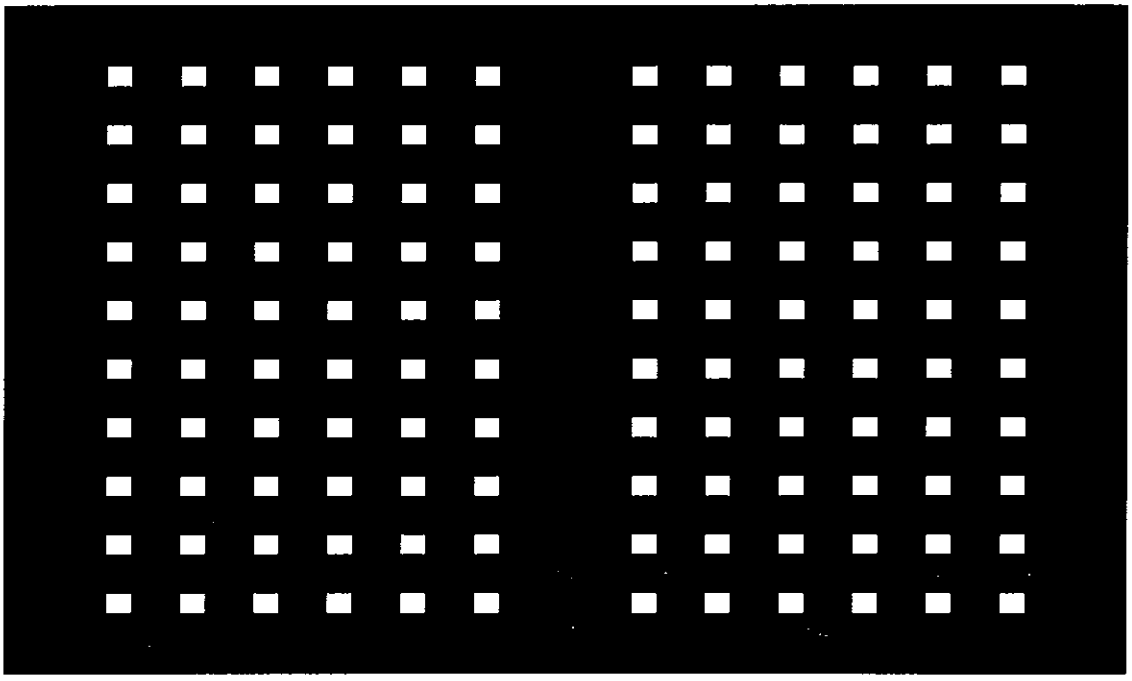


Figure 6.1: Flicker task requiring detection of a single target flickering at 16Hz surrounded by 119 identical non-flicker distractors

The displacement target was an empty white box (white lines of width 1 mm, subtending 7 minutes of arc, forming a square with an unfilled black centre), surrounded by identical stationary boxes as the distractors (Figure 6.2). The displacement target was displaced vertically by square-wave oscillation at 16 Hz through an angle of 14 minutes.

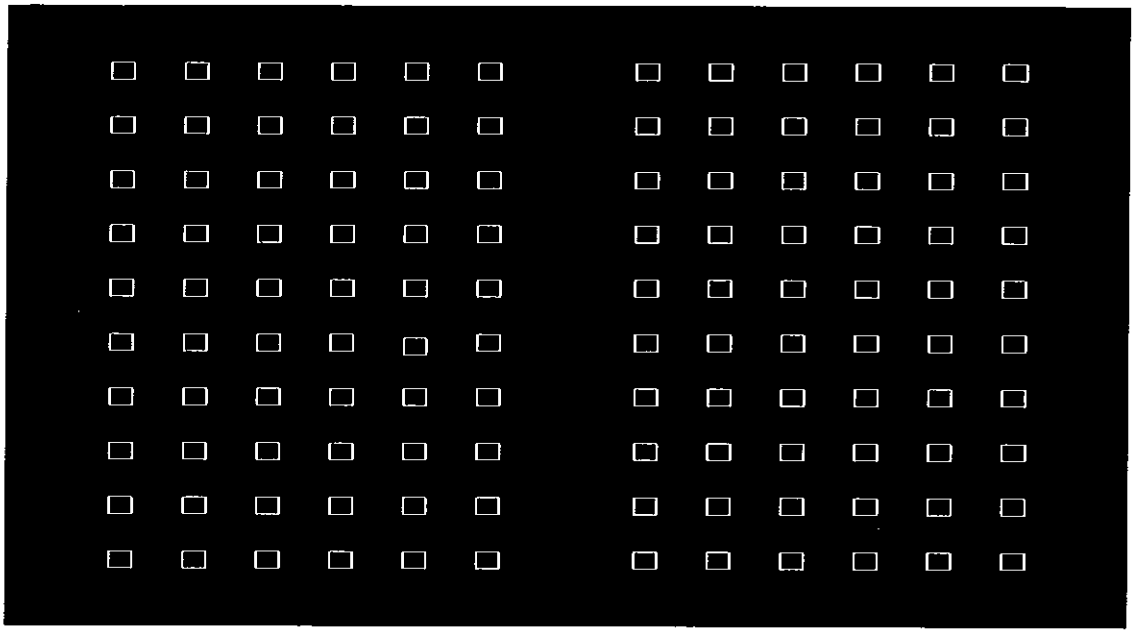


Figure 6.2: Displacement task requiring detection of a single target oscillating vertically @ 16Hz surrounded by 119 identical stationary distractors

The orientation target was the letter N surrounded by the letter Z as its distractor; both target and distractor limb widths were also 1 mm (Figure 6.3). Monitor resolution exceeded that required to present the lines forming the open boxes and N and Z targets.

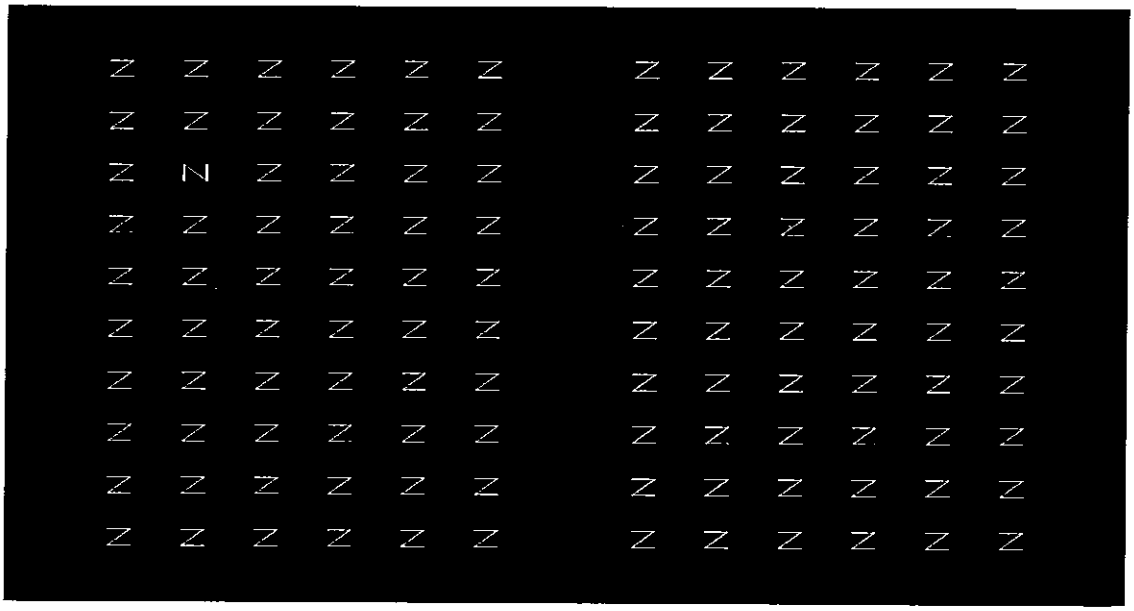


Figure 6.3: Orientation test target N surrounded by 119 distractors Z (representing a 90 degree orientation shift).

6.3 Test Strategy

Subjects were informed of the nature of the task and asked for their informed consent prior to test commencement (see Appendix 1 and 2). The subject was instructed to fixate a central fixation cross that appeared centrally between each presentation. The subject's task was to indicate using 2 handheld buttons, one in each hand, the target location, either on the left or right hand side of the screen; 60 stimuli were positioned either side of the central fixation cross and targets were presented randomly in any one of these 120 locations. PAVS response times were measured using a timer incorporated in the software (See Section 6.53). Subjects were asked to complete the task as quickly as possible without sacrificing accuracy. One eye was occluded for the duration of the test. Error responses (pressing the wrong button) were ignored in calculation of the mean response time. To ensure that fast-guessing was not a significant factor in the reaction time interpretation, subjects achieving less than 90% accuracy were excluded from the studies. Five seconds was the maximum time allowed to find any single target. All subjects were initially given a defined set of instructions on the requirements of the task (Appendix 2). This was followed immediately by a defined practice session for each target type (with the exception of certain subjects included in the experimental investigation of perceptual learning who were deliberately deprived of any practice period).

6.3.1 Reaction Time Paradigm

Clinical psychophysical tests of visual function are usually designed to evaluate a subjects' sensitivity to a particular stimulus or stimuli, and are generally designed to allow differentiation of normal from abnormal. The means of differential diagnosis varies according to the visual parameter under investigation. Most tests of visual function designed for glaucoma diagnosis rely on quantification of a subjects' visual

sensitivity at individual test locations using established thresholding strategies. The determination of the minimum stimulus of which a subject remains aware is however entirely unsuitable for a test of PAVS efficiency because feature differences must be large to facilitate pop-out. Target pop-out is an all-or-nothing phenomenon. If the stimulus is sufficiently different from its background in some basic dimension, it will be instantly detectable by functional preattentive mechanisms.

Traditionally the efficiency of visual search has been assessed by looking at changes in performance, generally on the basis of either reaction time (RT) or response accuracy (for set array display times) as a function of set size, which is the number of items in the display (Townsend, 1990). Such observed changes have then been used to make inferences about vision. The slope of the RT x set size function is the most commonly used measure of the efficiency of visual search (Wolfe, 2000). In parallel search, reaction time does not increase and accuracy remains high with increased set size. The current test employs a reaction time strategy. Rather than producing a slope of RT x set size, the set size remained constantly high (120 possible target locations) and the critical variables are a combination of reaction time and accuracy of determination of target location in a two-alternative forced choice paradigm. Green (1992) has previously demonstrated that subjects can localise (at least grossly) a pop-out target in parallel.

6.3.2 Simple and Choice Reaction Time Tests

Older adults exhibit limitations in the processing of information dependent on the type of task being undertaken. Simple reaction time (defined as the time from onset of a stimulus to onset of response) is little affected (Brebner & Welford, 1980) but a choice reaction time test which is slower and more difficult (Brebner & Welford, 1980) will

elicit a greater decrease in performance with age (Haywood & Getchell, 2001). Reaction times are composed of two major components. The first factor is the mental processing time which is the time required to (i) detect the sensory input from the object, and (ii) perceive and recognise the meaning of the sensation using integration with memory. The second factor is the movement time required to make the response. Once a response is selected, the responder must perform the required muscle movement (Green, 2000).

The reaction time strategy employed here therefore includes the time required to perceive the image, to localise the feature difference, to decide to respond with the appropriate location and finally to execute the hand/finger movement. Age has the potential to be a significant variable given the age profile of the glaucoma population.

The use of a reaction time paradigm instead of a thresholding strategy has significant benefits with regards to task simplicity and speed. It does however leave interpretation of data based solely on a subject's speed of response open to misdiagnosis were a subject's response time artificially increased due to non-visual functional defects. For example, a subject with severe chronic rheumatoid arthritis could conceivably have significantly increased response times due solely to poor manual dexterity in the absence of any loss of preattentive visual search efficiency. To account for similar potential sources of error (motor or neural), all subjects completed a simple reaction time (SRT) test and a choice reaction time (CRT) test (Figure 6.4).

The SRT test evaluates a subject's ability to simply react to the sudden appearance of a target on screen. It requires no complex processing or top-down search decisions and is

designed therefore to elucidate any loss of response time speed due to any physical or non-visual neural processing limitations.

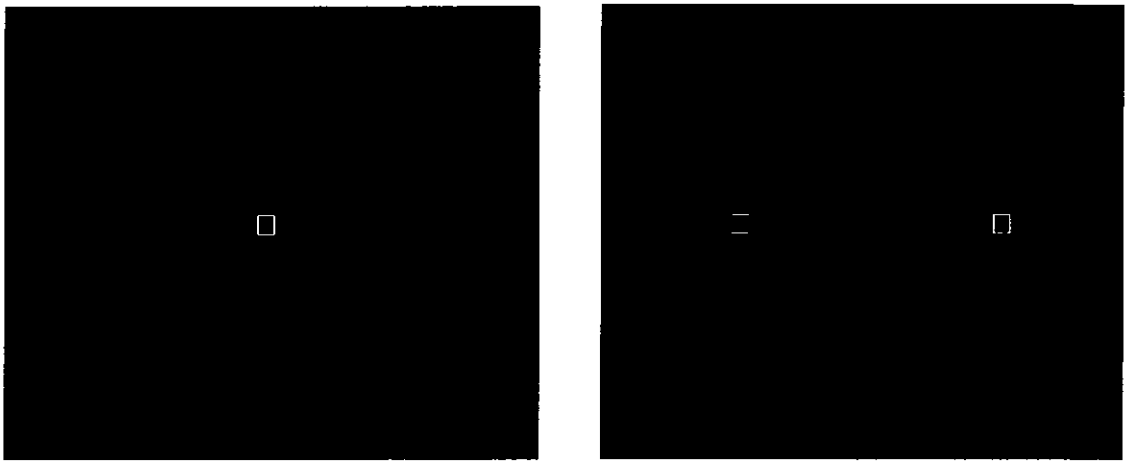


Figure 6.4: Simple (left) and choice (right) reaction time tests required a subject to respond (using a handheld button) to a stimulus onset after a variable time delay (during which the subject viewed a blank screen) between presentations. The simple test required only a response to stimulus presentation. The choice test required a decision as to location of the square.

The CRT test requires a subject to indicate the location of a specific target with only one distractor. As such it represents a quite primitive search task. If preattentive search efficiency is compromised, a decision can still be made following a rapid saccade at stimulus onset to one of two possible locations. A decision on target location can thus be made almost instantaneously. By its very nature, preattentive search times should not increase significantly above the CRT regardless of the number of distractors. The CRT therefore gives an indication as to the approximate PAVS time a subject should achieve given normal preattentive processing skills. It essentially indicates the timeframe an individual patient requires in order to make an appropriate choice as to target location and dividing the PAVS time by the CRT essentially renders the test independent of the potential variation with age in the sensory, attentional and motor

factors that contribute to the individual PAVS reaction time (see Chapter 8 for a more thorough review of the effects of age of visual search).

6.4 Stimulus Parameter Selection

The pop-out phenomenon is a psychological process involving the involuntary jerking of attention to an odd item (Nakayama, 1999). The fast and efficient processing of such highly important information probably evolved as an early warning survival mechanism and is most likely coded (for movement perception at least) by the more, transient and fast-conducting magnocellular pathway (Livingstone & Hubel, 1987b; Merigan et al., 1991).

Damage in glaucoma has been shown not to be confined to the magnocellular pathway in early glaucoma. Pattern discrimination perimetry (Drum et al., 1989a + b), high-pass resolution perimetry (Frisen, 1987), colour discrimination (Sample et al., 1986) and short wavelength automated perimetry (Johnson et al., 1993a) have all detected functional losses in early glaucoma.

The current PAVS test also allows rapid and easy stimulus configuration during the course of a single examination, enabling preferential stimulation of cells with different optimal sensitivities. The current test presents a flicker and displacement target both modulated at 16Hz to preferentially stimulate the magno-pathway, and a high spatial frequency orientation target to preferentially stimulate the parvo-pathway (these frequencies can all be readily altered). Given the apparently non-selective nature of retinal ganglion cell death in glaucoma, it would seem desirable to evaluate the functional integrity of different cell types during the course of an examination to optimise sensitivity to the earliest losses in glaucoma.

A test of PAVS efficiency is inherently different from conventional psychophysical techniques. Such techniques characteristically rely on the presentation of single targets in isolated areas of the visual field. The current test presents 120 stimuli and relies on the detection of a feature difference. As such it requires retinal integration of the combined responses of neighbouring and overlapping receptive fields of retinal ganglion cells. Such a strategy potentially overcomes the receptive field overlap problem and studies have confirmed that other population-response tests such as motion coherence (Silverman et al., 1990) and pattern-discrimination perimetry (Drum et al., 1989a; 1989b; Nutaitis et al., 1992; Chauhan et al., 1993) are possibly more sensitive than standard achromatic perimetry.

Thus, the stimuli and test design are such that it may be possible to detect the earliest signs of glaucomatous visual loss irrespective of the type of cell affected or loss induced.

6.5 Software Development

The original software program is one designed and written by Dr. Ian Flitcroft to investigate the sensitivity of a preattentive visual search test in detection of glaucoma. The version used throughout the experimental data collection of the current project is largely similar to that initially used by Dr. Flitcroft in his early investigations (Flitcroft et al., 1996). A number of notable changes however have been made to the software program by Mr. James Callis at our request. The following is an account of such changes and the rationale behind them.

6.5.1 Displacement and Orientation Target Changes

Experiment 1 ended with the conclusion that the orientation target was simply unsuitable in its current form to be of diagnostic use on patients with subnormal visual acuity (see Chapter 7). As glaucoma predominantly affects the over 40 year old age group, it is entirely likely that a significant percentage of these patients will have subnormal acuity due to other factors, e.g. media opacities which become more prevalent with age (as does glaucoma). Therefore it was decided to attempt to develop a more suitable orientation target with lower spatial frequencies similar to that contained within the flicker target. Several versions were designed and tested for improved resistance to optical blur (see Chapter 7 for results). Figure 6.5 illustrates the initial target change to a lower fundamental spatial frequency/increased limb width (limbs now subtending 14 minutes of arc – Snellen Equivalent ~6/18). Given that sensitivity to lower and medium spatial frequencies remains less affected by optical blur, and that the visual system is most sensitive to medium spatial frequencies (see Figure 2.10 –Blakemore & Campbell, 1969), it seemed a logical step to explore the possibility that such a change might improve resistance to blur.

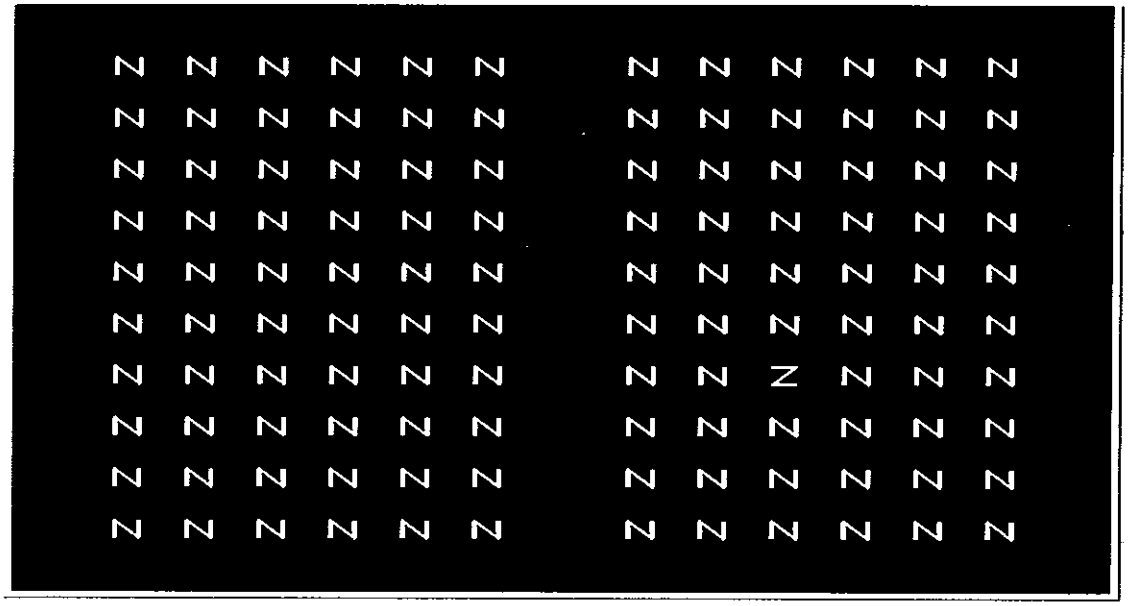


Figure 6.5: The initial design change maintained the same target/distractor type but with increased limb width/lower fundamental spatial frequencies

Figure 6.6 illustrates a complete target design change in an attempt to determine whether a new target/distractor combination (also with increased limb width subtending 14 minutes arc) at a 45-degree rather than 90-degree orientation difference might elicit improved performance under blurred conditions.

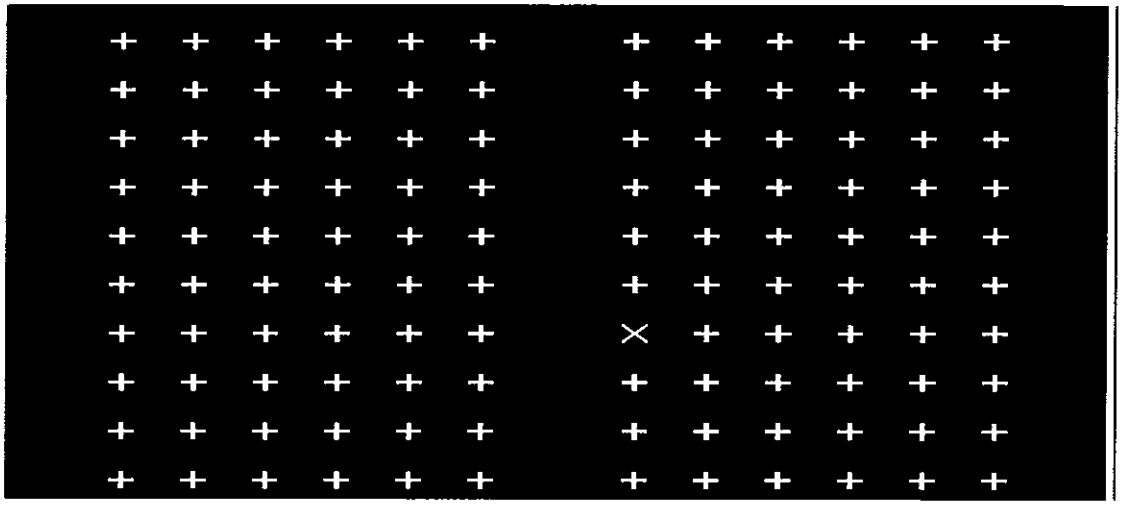


Figure 6.6: Target shape change and orientation difference change

Figure 6.7 illustrates a more radical target/distractor design change. The spatial frequency is obviously lower and the distractor shape matches that used in the flicker task (Figure 6.1). Thus orientation search efficiency was explored across a range of stimulus sizes, spatial frequencies and designs (see results in section 7.6.2).

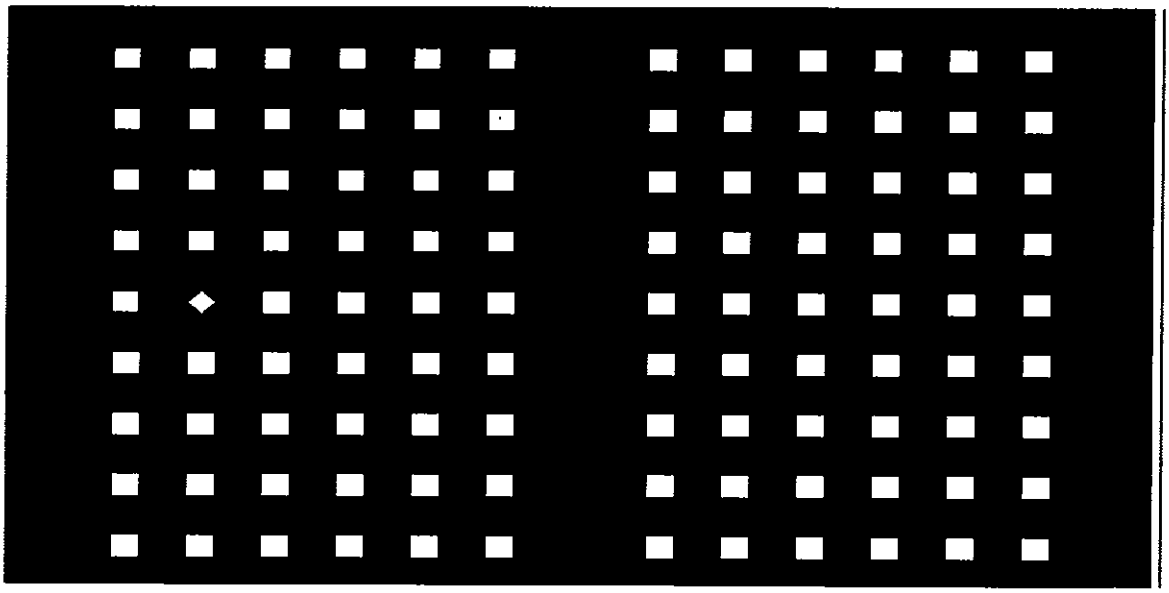


Figure 6.7: Diamond target orientation among square distractors

The vertical displacement target, while significantly more resistant to lower degrees of blur than the orientation target (see Chapter 7), was not fully resistant. To rectify this, the target was altered from an empty box configuration (Figure 6.2) to that of a filled box identical to that used in the flicker task (Figure 6.1).

6.5.2 Choice and Simple Reaction Time Tests

The rationale and target designs (Figure 6.4) are covered in section 6.3 above.

6.5.3 System Timer

The PAVS program originally used a software loop to produce the flicker/displacement rates. This meant that the timing accuracy could only be guaranteed for a specific computer (PC). Running the program on a faster/slower computer would require a change to the number of iterations of the software loop to compensate for the greater/slower processing speed of the PC. This was an obvious design flaw that would complicate the use of the program in multiple locations. By using the PC's system hardware directly it was possible to implement a timer with theoretical resolution of 1 microsecond. All timings within the PAV program now use this high-resolution timer (all experiments except the investigation of optical blur used this improved timer). In practice there is a delay of 10-30 microseconds (the time it takes to read the value), so timed events may have an error of up to +30 microseconds. This timer is also independent of the speed of the computer used.

6.5.4 Data Display

The initial design left data interpretation difficult and rather messy (Figure 6.8). To resolve this, the data display was reorganised in a columnar design indicating readily the quadrant presented, the response time, and whether the response was correct or

incorrect for each presentation across each task. A mean response time and standard deviation was also computed and automatically reported (Figure 6.9). The percentage of correct responses is also reported to allow an immediate impression as to the acceptability of the test result. A response time paradigm can obviously be affected by "button pressing" where subjects choose to guess the location rather than search for it if PAVS mechanisms are not intact. Failure to identify the percentage of incorrect responses could mask such an effect invariably leading to an underestimation of the extent of loss of efficiency of PAVS in any particular subject.

```
NAME:                    NUMBER:           Eye:  R / L
AGE:                     COMMENTS:
No. Elements      120,         Mean Reaction Time      0.588
Trials              40,         Correct Trials      40
Max Lum     63,          MinLum      33,Loop Delay     118
Data #1
550, 550, 820, 440, 440, 440, 440, 490, 720, 500, 550, 550, 430, 990,
2580, 490, 770, 550, 440, 500, 490, 600, 380, 770, 380, 500, 440,
430, 660, 390, 380, 390, 710, 440, 440, 610, 440, 720, 660, 440,
3, 2, 1, 0, 3, 0, 2, 0, 1, 3, 1, 0, 2, 3, 1, 0, 2, 1, 2, 3, 2, 1, 3,
1, 3, 0, 2, 0, 1, 2, 0, 2, 1, 3, 0, 3, 2, 3, 1, 0,
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
0, 20, 15, 4, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
No. Elements      120,         Mean Reaction Time      0.487
Trials              40,         Correct Trials      37
Pixel Movt  3,           Loop Delay  237
Data #2
1370, 490, 330, 720, 930, 500, 330, 660, 380, 500, 330, 710, 330,
380, 330, 390, 330, 390, 820, 320, 380, 330, 320, 660, 500, 430, 380,
440, 650, 380, 380, 600, 440, 500, 390, 380, 380, 380, 600, 380,
1, 0, 2, 3, 1, 0, 2, 1, 2, 3, 2, 1, 3, 1, 3, 0, 2, 0, 1, 2, 0, 2, 1,
3, 0, 3, 2, 3, 1, 0, 3, 2, 1, 0, 3, 0, 2, 0, 1, 3,
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
0, 1, 1, 1, 1, 1, 1, 1, 1, 0, 1, 1, 1, 1, 1, 1, 1,
0, 24, 10, 2, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
No. Elements      120,         Mean Reaction Time      0.507
Trials              40,         Correct Trials      39
Background Pattern      6,           Test Pattern      8
Data #3
440, 490, 660, 600, 440, 1050, 550, 550, 500, 490, 550, 500, 540,
440, 550, 440, 600, 440, 500, 500, 440, 440, 440, 440, 440, 440, 660,
440, 440, 500, 380, 390, 770, 490, 550, 650, 500, 330, 430, 330,
2, 0, 1, 2, 0, 2, 1, 3, 0, 3, 2, 3, 1, 0, 3, 2, 1, 0, 3, 0, 2, 0, 1,
3, 1, 0, 2, 3, 1, 0, 2, 1, 2, 3, 2, 1, 3, 1, 3, 0,
1, 1, 1, 1, 1, 1, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
```

Figure 6.8: Example of the initial data presentation design proved cumbersome to inspect

RIGHT EYE **TRIALS:10** **ELEMENTS:120**

[TASK 1 FLICKER TEST] **[TASK 2 MOVEMENT TEST]**

MIN LUMINENCE:33 PIXEL MOVEMENT:3

MAX LUMINENCE:63 MOVEMENT FREQ (Hz):32

FLICKER FREQ (Hz):32

[TASK 3 ORIENTATION TEST] **[TASK 4 SIMPLE RT]**

BACKGROUND FIGURE: Z **[TASK 5 CHOICE RT]**

TEST FIGURE: N

	TASK 1	TASK 2	TASK 3	TASK 4	TASK 5
1	4390 1 1	5000 1 0	5000 1 0	500 1 2	2640 1 2
2	2140 1 3	5000 1 3	3130 1 3	380 1 0	880 1 0
3	3730 1 1	5050 1 2	2740 1 2	380 1 1	550 1 3
4	1040 1 3	4340 1 3	5050 1 1	430 1 3	1260 1 1
5	5000 1 0	5000 1 1	1100 1 0	380 1 2	1650 1 1
6	1930 1 2	5000 1 0	1540 1 3	440 1 0	710 1 3
7	1540 1 0	5050 1 3	2360 1 0	500 1 1	550 0 0
8	1370 1 1	2910 1 2	1380 1 2	440 1 0	710 1 2
9	1160 1 2	3410 1 1	720 1 0	430 1 3	1100 1 0
10	1530 1 0	5000 1 0	5000 1 1	820 1 1	940 1 3
MEAN	2383	4576	2802	470	1099
SDEV	1368	744	1608	1270	123	606
% CORRECT	100	100	100	100	100

Figure 6.9: Reconfigured columnar display for the basic test (differs from that used for the eccentricity analysis - see Figure 6.10) showing (from left to right) presentation number, response time in milliseconds, correct/ incorrect response (1 = correct; 0 = incorrect) and presentation quadrant (0 = top left; 1 = bottom left; 2 = top right; 3 = bottom right).

6.5.5 Eccentricity Effects Analysis

In the normal test configuration, the position of a target among the surrounding distractors varies in a random manner throughout the total number of presentations. The only prerequisite is that there are an equal number of presentations in each quadrant. The data file gives no indication as to the precise location of each target presentation, isolating each only to a particular quadrant. This meant that precise positional information necessary for any investigation of the effects of eccentricity on PAVS performance was not available.

The software was thus reconfigured to allow precise determination of the location of each target presentation along with all the other information gathered (Figure 6.10). In this version of the program, the position of the stimulus is now non-random. Stimulus position is determined by a table read from a file called POS.CSV which is read each time the program is run. This program was used for the experiment in Chapter 10. The format of the POS.CSV file is as follows: QUADRANT, X, Y

The QUADRANT location can have values between 0 and 3 arranged as follows (as in Figure 6.9). 0 2

1 3

X,Y specifies the position within each quadrant (divided into 6 columns (X) and 5 rows (Y)) Z Z Z Z Z Z

Z Z Z Z Z Z

Z Z Z Z Z Z

Z Z Z Z Z Z

Z Z N Z Z Z The target (N) is at position 3,5

	TASK 1			TASK 2			TASK 4
		Q	X Y		Q	X Y	
1 |	990	0	[0,0,0]	660	0	[2,5,2]	270
2 |	770	1	[0,1,1]	440	1	[2,5,1]	220
3 |	380	1	[0,2,2]	440	0	[3,2,2]	220
4 |	330	0	[0,3,3]	280	0	[3,2,2]	220
5 |	600	0	[1,0,0]	390	0	[3,2,2]	220

Figure 6.10: Eccentricity analysis display includes the response time and precise positional information for each display.

6.6 Conclusion

The current PAVS test has thus been modified and developed to the extent that it is significantly more robust and more suitable for additional experimental designs. It is by no means the ultimate package but may provide the framework for future versions employing similar or enhanced designs.

CHAPTER 7

EFFECT OF RETINAL IMAGE DEGRADATION ON PRE-ATTENTIVE VISUAL SEARCH (PAVS) EFFICIENCY FOR FLICKER, VERTICAL DISPLACEMENT AND ORIENTATION STIMULI

7.1 Summary

Background: The purpose of the research reported here was to examine for the first time the resistance of PAVS to optical blur using targets differing from the background in terms of flicker, vertical displacement, and orientation. Resistance would enhance the applicability of PAVS as a screening method for glaucoma and other clinical conditions affecting performance of a substantial area of the retina. Lack of resistance would mean a requirement for optical correction or a minimal visual acuity criterion for valid test completion

Method: Computer generated flicker, orientation, and vertical displacement targets were used to assess PAVS efficiency. Average PAVS response times were calculated for 40 presentations of each target type presented randomly in any one of 120 positions within +/- 15 degrees of fixation. 17 subjects performed the test using their distance spectacles (unless emmetropic), then 3 tests using positive lenses simulating myopia up to - 3D, and finally using distance spectacles again. Nine subjects were cyclopleged to permit assessment of PAVS performance in simulated presbyopia. All subjects also completed a simple and choice reaction time test.

Results: One-way ANOVA revealed that blur of up to 3 dioptres had no statistically significant effect on response times to the *flicker* target. Blur of over 2.0 D however resulted in increased response times for the *displacement* target, but only for eyes which were not cyclopleged. The *orientation* target became significantly more difficult to locate, response times becoming progressively slower with increasing levels of blur ($p<0.05\%$). Modifications to the displacement target achieves complete resistance to the effects of optical blur, while attempts to reduce the effect of blur on the orientation

target through numerous target modifications failed to produce any improvement in performance under blurred conditions.

Conclusions: The present flicker and displacement targets are relatively resistant to the effects of reduced acuity, while the orientation target is only suitable for testing subjects with good visual acuity.

7.2 Introduction

Pre-attentive vision implies parallel processing by the visual system on multiple target features simultaneously (Townsend, 1990; Treisman, 1985). Several studies have shown that the search for a target pattern among distractor (non-target) patterns is fast and parallel once this target differs significantly from its background in some basic stimulus dimension (Nakayama & Silverman, 1986; Nothdurft, 1991; Nothdurft, 1993; Saarinen, 1996). A pre-attentively detected stimulus appears to "pop-out" (Saarinen, 1996) and this pop-out allows very rapid detection of a target among a field of distractors before a saccadic eye movement can be made.

One can assume that the recorded mean visual search times of between 0.4 and 0.7 seconds without blur in the present study in the presence of 119 distractors indicates that search is pre-attentive for the tests used here. Previous studies indicate typical mean search times of approximately 0.5 seconds for simple feature (rather than conjunction) search tasks (Treisman, 1985; Saarinen, 1996; Wolfe, 2000). Support for this assumption comes from two findings.

Firstly, if one assumes that 20 milliseconds search time or greater per display item provides a working definition of serial search (Wolfe, 2000), one would expect the

serial search time for a single target among 120 items to take up to 2.4 seconds and lead to significantly more variance in response times. This value was never exceeded with flicker or displacement targets regardless of degree of blur though mean response times did exceed this value for the orientation target with 3 dioptres of induced blur.

Secondly, a commonly assumed feature of pre-attentive visual search is that search time is almost independent of the number of distractors. In this context we found that the mean simple and choice reaction times using just 2 targets but otherwise identical conditions (0.31 and 0.40s respectively) are close to those obtained using our PAVS paradigm with 119 distractors (e.g. 0.47s for the displacement target without dioptric blur).

Recently, several studies have looked at potential applications of the PAVS technique to detection and diagnosis of clinical conditions, including glaucoma (Flitcroft et al., 1996), Parkinson's disease (Troscianko and Calvert, 1993) and dementia (DLB) with Lewy bodies (Cormack et al. 2004). In Flitcroft's case, the authors reported that the three tests in their battery of PAVS tests successfully discriminated between patients with and without glaucoma. Flicker and motion targets, as used by Flitcroft et al. have been shown to be sensitive to glaucoma in a conventional single target psychophysical (non- visual search) environment (Tyler, 1981; Fitzke et al., 1987). The PAVS response time paradigm as used here has potential advantages over flicker perimetry in terms of speed and being easily understood by patients.

Other clinical studies using PAVS include Troscianko and Calvert (1993) who found that pop-out using a bar-shaped target differing in orientation from its distractors was impaired in Parkinson's disease. In Cormack et al.'s 2004 study, the task was to detect

a red target embedded in green distractors. While PAVS was found to correlate with DLB dementia, choice reaction time showed no correlation.

To date little attention has been paid to the potentially complicating effects of retinal image degradation on search performance. Thus false positive results could conceivably be expected if a PAVS test, used for screening purposes, is too sensitive to optical blur simply because a patient is not wearing an optical correction when taking a PAVS test. Screening for glaucoma and other conditions must sometimes be performed in circumstances where visual acuity is reduced for purely optical (defocus) reasons.

The purpose of the study reported here was to examine the resistance of PAVS to dioptric blur using targets differing from the background in terms of flicker, displacement, and orientation since to our knowledge this has not been previously examined. The present study (sections 7.3 to 7.5) has been published elsewhere (Loughman & Davison, 2002; Davison & Loughman, 2006). One might expect the former two conditions to show some resistance to defocus, based on findings with conventional psychophysical targets (**flicker:** Lachenmayr and Gleissner, 1992; **displacement:** Whitaker & Buckingham, 1987). Similarly, one might expect the orientation target, being essentially an acuity target, to show a predictable lack of resistance. However, the nature of PAVS tasks is clearly very different from conventional psychophysical tests. The purpose of the present study was to examine whether similar effects occur for PAVS tasks. Resistance to dioptric blur would enhance the applicability of PAVS testing to glaucoma and other clinical conditions affecting performance of a substantial area of the retina, while lack of resistance would

increase the expected incidence of false positives if PAVS were to be used for clinical screening.

In this study PAVS stimuli have been employed where the difference between target and distractors is high as a supra-threshold environment is generally more effective for visual screening purposes, as for example in testing of visual fields (Henson and Agnihotri, 1995). The use of a response time here, rather than threshold experimental paradigm, also simplifies the nature of the PAVS test from the subject's point of view. This has potential advantages if the test is to be applied to patients with limited span of attention, including elderly patients amongst whom most types of glaucoma are most prevalent (Klein et al., 1992).

7.3 Method

(a) *Subjects*

17 adults ranging from 16 to 22 years (mean = 18 years) were tested, all being normal according to the following criteria: no history of treatment for or family history of glaucoma, normal optic nerve and retinal nerve fibre layer (assessed by direct ophthalmoscopy), wide open anterior chamber angle (van Herick's technique, using a slitlamp biomicroscope), and intra-ocular pressure < 21mm Hg. (mean of 3 readings with the Pulsair non-contact tonometer). All subjects were judged to be free from glaucoma and ocular hypertension on this basis; these are necessary exclusions since Flitcroft et al. (1996) have shown PAVS to be affected by both conditions. All subjects achieved logMAR 0 (6/6) or better visual acuity on a Bailey-Lovie test chart.

(b) Apparatus and Stimuli

The apparatus and stimuli used were previously described in section 6.2. The subject's task was as described in section 6.3. Error rates were less than 5% for each subject.

(c) Procedure

Unaided vision was first recorded using a Bailey-Lovie chart. Cyclopentolate (0.5% w/v) was instilled in one eye of some subjects, usually the right eye, unless circumstances dictated otherwise. Subjective refraction and retinoscopy were performed on all subjects to ensure accurate correction of ametropia. All subjects were subjected to the same order of presentation of stimulus conditions, as indicated below, including a "no blur" condition at the beginning and again at the end of the test procedure. The eye not under test was occluded while the eye under test was optically corrected where necessary. The subject was shown a demonstration of each PAVS task, and instructed to press the relevant button as quickly as possible, once the target location was identified. The subject was allowed two full practice runs through each task, a total of 240 presentations, to ensure that subjects had reached a learning plateau (Ahissar & Hochstein, 1996).

The subject then began the test proper, firstly for the flicker target, followed by the displacement and then finally for the orientation target, through the distance optical prescription (Rx) if any. Each single test consisted of 40 presentations of each target type, initially without optical blur (condition "no blur 1"). Once completed, the most positive blurring lens to be used was put in the trial frame and the test was completed again (using a +5.00 D lens to create 3.00 D blur at a fixation distance of 50cm). Two further lenses were used to produce blur of 2.00 D and 1.00 D respectively. Blurring was confirmed using a near visual acuity test chart at 50 cm (the viewing distance for

the monitor) prior to PAVS testing. Examining the subject once more with only the distance Rx in place completed the test (condition "no blur 2").

Of the 17 subjects, 9 were tested with the use of cyclopentolate to induce cycloplegia, and the other 8 were not. For the cyclopleged subjects, +2.00 D spheres were used to create the "no blur" condition at 50 cm; the lenses required to produce blur were in addition to this value. For cyclopleged subjects an additional condition was presented: 2.00 D of simulated presbyopia, i.e. no spherical lens when viewing the monitor at 50 cm without accommodation.

7.4 Results

One-way repeated-measures ANOVA was used separately on the cyclopleged and non-cyclopleged groups. The results for "no blur 1" and "no blur 2" reflect the condition of clear focus on the screen at 50 cm from the eye, either dependent on accommodation for those tested without cycloplegia or using a +2.00 D lens for those with cycloplegia induced.

7.4.1 Flicker

Figures 7.1 and 7.2 show that simulated myopia, induced by plus lenses, had little effect on the ability of visual search mechanisms to detect and locate the flickering target among its distractors for subjects with or without cycloplegia. Repeated-measures ANOVA was performed separately for non-cyclopleged and cyclopleged subjects since the number of conditions were different for the two groups. Variance across "no blur 1" and all blur conditions were non-significant for both non-cyclopleged subjects ($F=3.366$, $dF=7$, $p=0.112$) and cyclopleged subjects ($F=2.098$, $dF=8$, $p=0.219$). PAVS reaction times were slightly faster with 1D blur than with "no

blur 1"; the difference may reflect a learning effect but was not statistically significant (t= -2.01, p>5%).

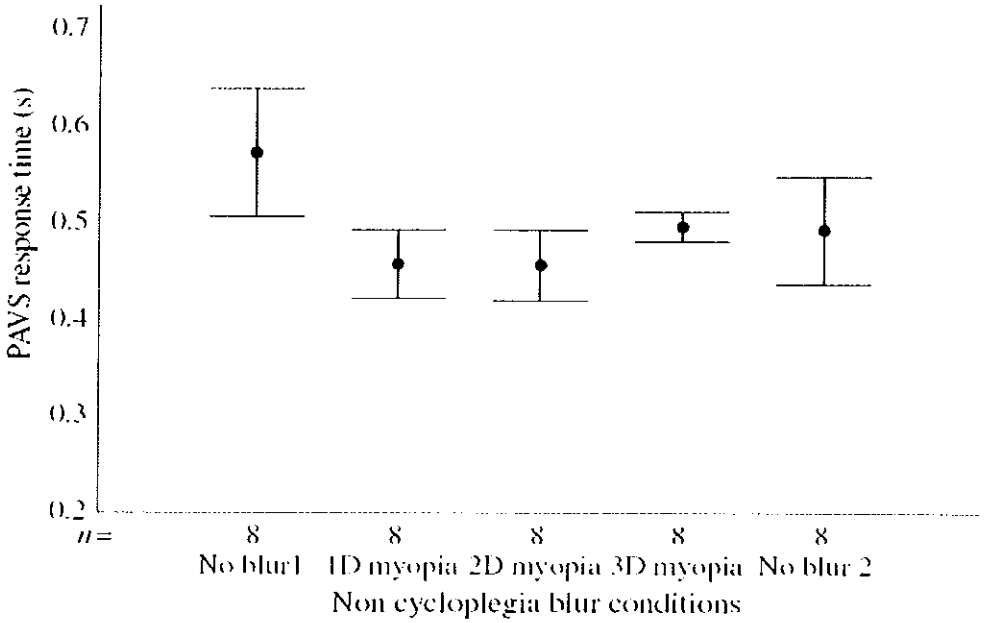


Figure 7.1: Effect of simulated ametropia on PAVS times: flicker target, non-cyclopleged eyes.

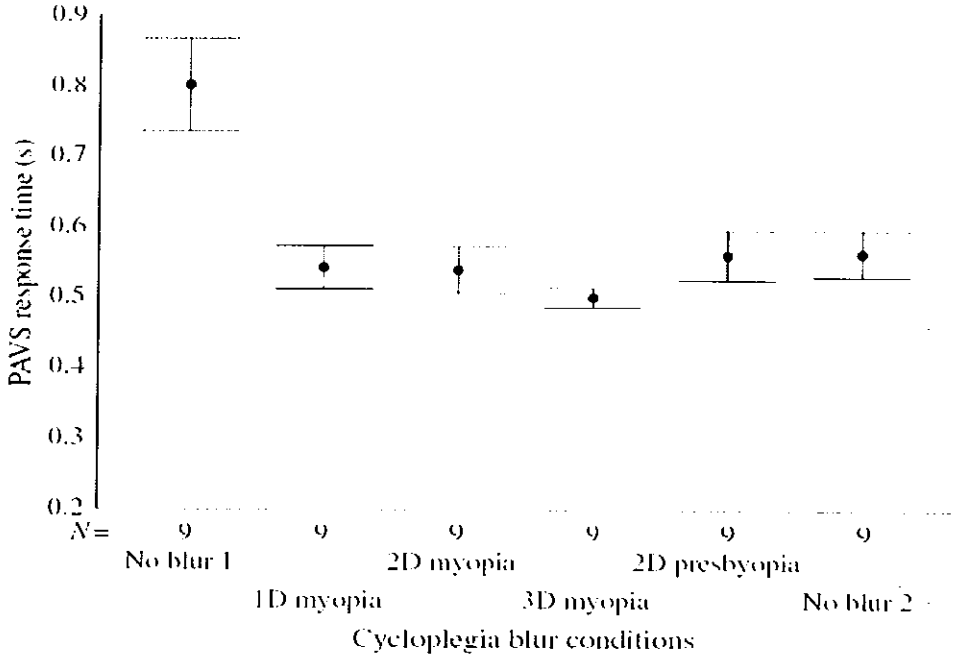


Figure 7.2: Effect of simulated ametropia on PAVS times: flicker target, cyclopleged eyes.

7.4.2 Displacement

ANOVA results for the displacement target across all levels of blur were non-significant for both non-cyclopleged subjects (F=5.081, dF=7, p=0.056) and cyclopleged subjects (F=3.372, dF=8, p=0.107). However, Figures 7.3 and 7.4 suggest no significant increase in mean response times to a displacement target under blurred conditions up to 1 D for both groups, but increased response times for levels of blur above this for the non-cyclopleged group only. Post-hoc paired t testing for this group revealed an effect for 2 D or more of blur. Thus while a non-significant difference occurred between "no blur 1" and 1 D blur (t=-1.586, p=0.157), a significant increase in response times occurred for 1 D blur versus 2D blur (t=-3.473, p=0.010).

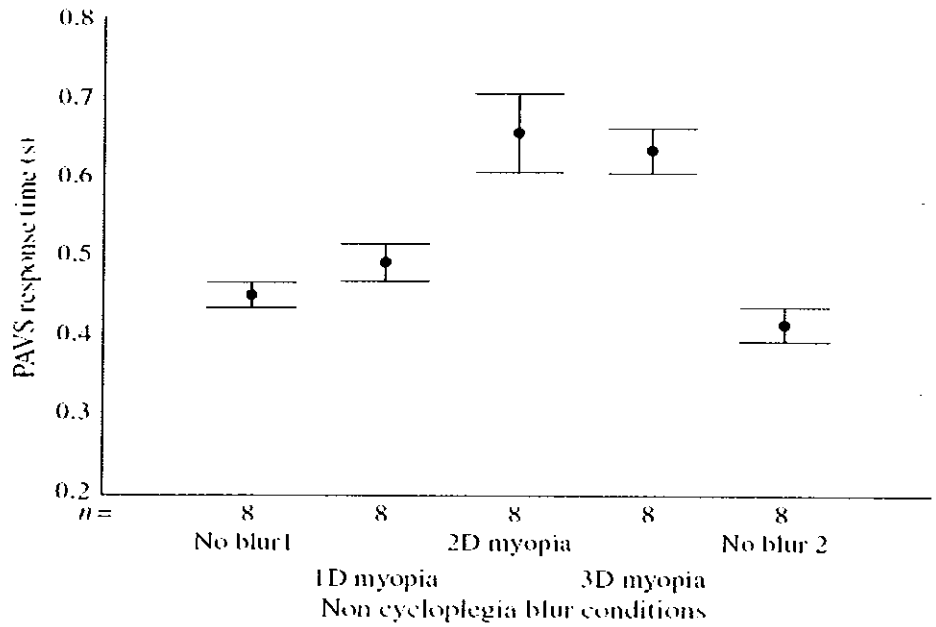


Figure 7.3: Effect of simulated ametropia on PAVS times: displacement target, non-cyclopleged eyes.

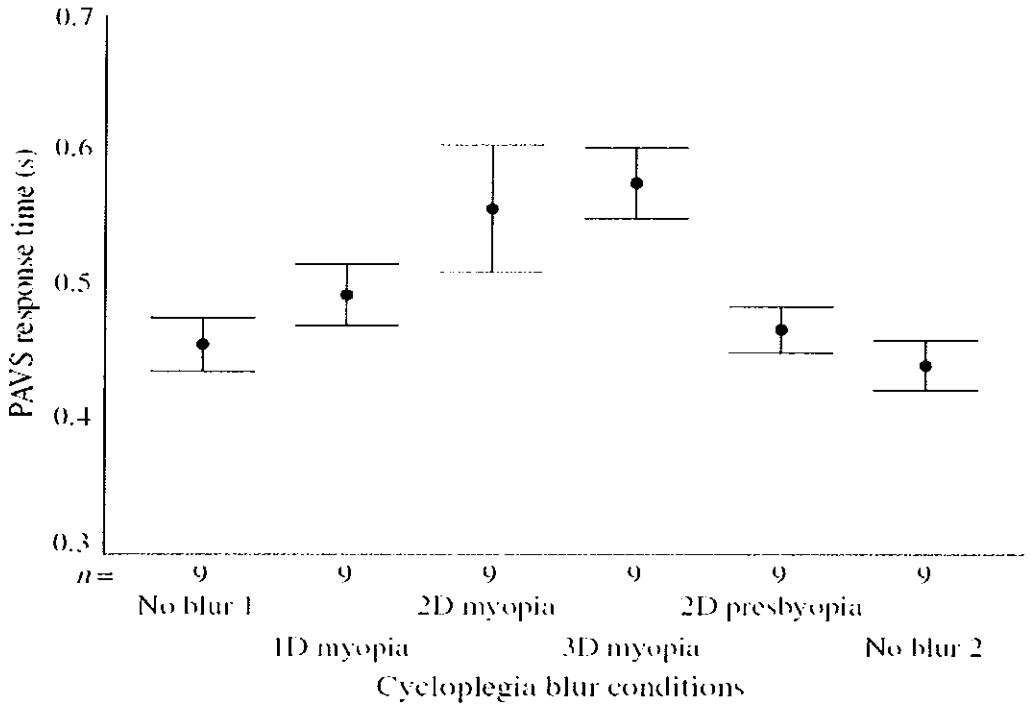


Figure 7.4: Effect of simulated ametropia on PAVS times: displacement target, cyclopleged eyes.

7.4.3 Orientation

Figures 7.5 and 7.6 suggest that the orientation target (N surrounded by Z distractors) was far less resistant to blur than either flickering or displacement targets. Response times increased with increasing levels of simulated myopia and ANOVA revealed the increase to be statistically significant for both non-cyclopleged eyes ($F=77.075$, $dF=7$, $p<0.001$), and cyclopleged eyes ($F=484.567$, $dF=8$, $p=0.017$). Post-hoc paired t testing for non-cyclopleged eyes revealed the same effect for both groups, with significant differences occurring even between "no blur 1" and 1 D of induced myopia ($t= 4.471$, $p= 0.010$). For cyclopleged subjects, there was no significant effect at 1 D of blur ($t=2.0078$, $p=0.071$), but a significant increase in response times did occur at 2 D ($t=4.136$, $p=0.003$).

The mean response times for subjects tested under conditions of simulated myopia of 2D or more were dramatically increased, with mean response times increased with 2D blur by 1.23 seconds for non-cyclopleged eyes and by 0.99 seconds for cyclopleged eyes compared to the initial "no blur 1" condition, indicating a breakdown of parallel search, and a changeover to serial search mechanisms.

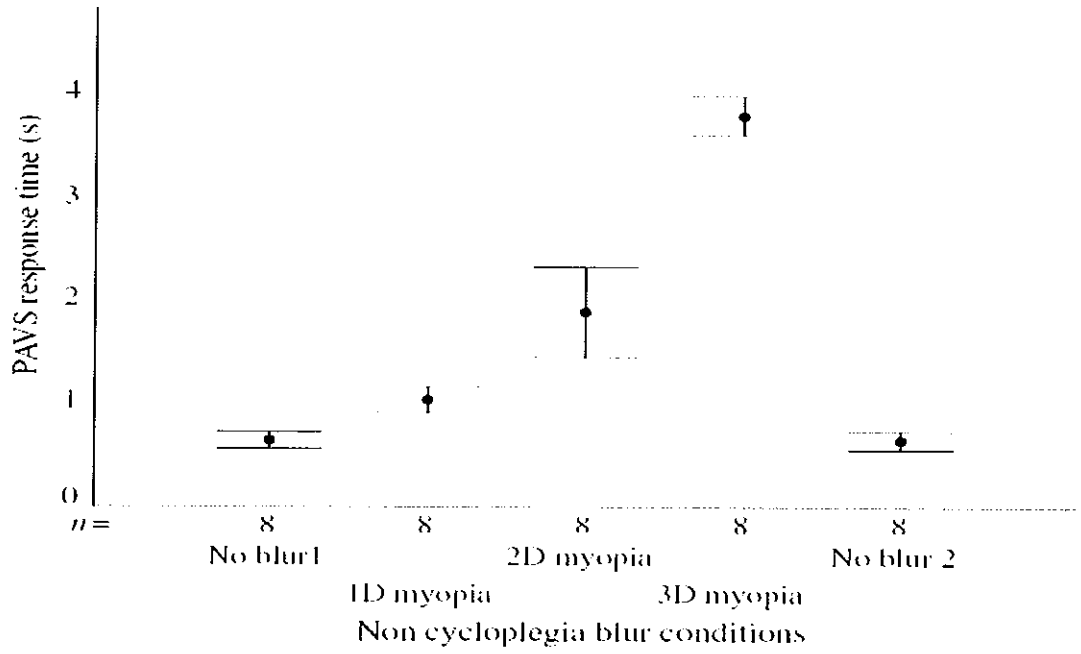


Figure 7.5: Effect of simulated ametropia on PAVS times: orientation target, non-cyclopleged eyes.

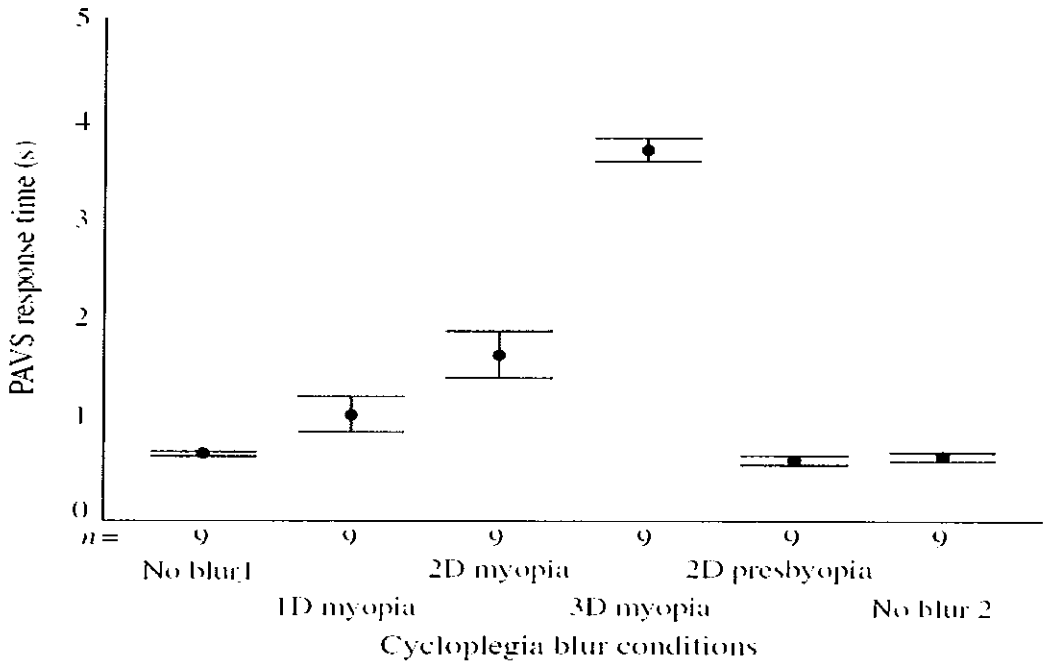


Figure 7.6: Effect of simulated ametropia on PAVS times: orientation target, cyclopleged eyes.

7.5 Discussion

The finding that the presence of even 3 dioptres of blur has no statistically significant effect on visual search efficiency for a flickering target is possibly related to the fact that the distractors are out of focus and the flickering target is apparently the most visible stimulus to subjects due to its flickering nature, even though blurred on screen, such that search remains efficient despite substantial blur. Therefore it can be assumed that a high level of acuity may not be necessary to complete the flicker task efficiently. This finding of resistance to blur using a PAVS paradigm is similar to that obtained with flicker perimetry thresholds (Lachenmayr & Gleissner, 1992). The relevance of flicker detection thresholds, as distinct from visual search time for a flickering stimulus, to glaucoma has been shown previously (Tyler, 1981).

By contrast, the displacement target produced longer response times, possibly because of its nature – an empty box (containing no low fundamental spatial frequencies)

compared to a filled white box for the flicker task. It is well known that targets containing only high spatial frequencies are degraded by blur (e.g. Charman & Jennings, 1976). The resistance to blur of up to and including +2 dioptres for displacement targets for non-cyclopleged eyes, is similar to that reported for oscillatory movement detection thresholds (Whitaker and Buckingham, 1987), a technique with potential application for evaluation of retinal integrity behind a cataract (Barrett et al., 1994). The validity of movement detection thresholds to glaucoma has been noted for oscillatory movement thresholds of a line target by Fitzke et al. (1987), and for random dots by Silverman et al. (1990) and Bullimore et al. (1993).

However, analysis of results for the cyclopleged eyes using ANOVA showed no significant effect of blur up to 3 dioptres on response times. The statistical difference for displacement targets between cyclopleged and non-cyclopleged eyes is presumably associated with the larger variance in the data for cyclopleged eyes. The decreased depth of field with dilated pupils in the former case should have increased, and not decreased susceptibility to dioptric blur.

One can conclude that, within the limits of this experiment, optical defocus of up to and including 2 dioptres will have little or no detrimental effect on visual search efficiency for flicker and displacement targets and would probably not lead to false positive results when screening for glaucoma, in which much more substantial increases in response times have been reported (Flitcroft et al., 1996). However the displacement target requires modification to increase its spatial frequency bandwidth to the same level as that of the flicker target to improve its resistance to blur beyond 1.5 dioptres (see section 7.6 below).

The orientation test employed a stationary target. While orientation differences are a strong stimulus to parallel search mechanisms (Wolfe, 1996), the ability of these mechanisms to locate the N among the Z distractors, was significantly reduced by the simulated myopia. The higher the degree of ametropia induced, the more inefficient search became. The lines comprising the targets subtended 7 minutes at the eye, 9 times the Rayleigh resolution limit of 47 seconds assuming light of wavelength 555 nm and a pupil diameter of 3mm. Given a typical ten-fold loss of acuity (6/6 to 6/60) with uncorrected ametropia of 2.00 dioptres one would expect the lines comprising the Ns and Zs to lose visibility with this amount of optical defocus in the present experiment. Both the target (N) and the distractors (Z) were out of focus to the same extent and, because of this, the visual system was apparently unable to decipher the orientation difference, and therefore unable to locate the target efficiently. It might be presumed that foveal search is required and the response time slows accordingly.

Interestingly in this context, Carrasco et al. (1998) reported that PAVS response times are significantly longer for higher (10 cycles per degree) than lower (2 cpd) spatial frequencies for gratings embedded in Gabor patches within a central 14 degree field. The lines comprising the N and Z targets may be considered as elements of square wave gratings with a fundamental spatial frequency of 4.3 cpd. However, initial observations suggest that broadening the line width appears not to reduce response times under blurred conditions (see section 7.6 below).

In general it can be seen that for both the flickering and displacement targets, simulated ametropia of up to 2.00D did not interfere with visual search efficiency in that ANOVA showed no statistically significant increase in mean response times across all blur levels. Indeed a relative enhancement of performance occurred when

the distractors were sufficiently out of focus even at levels of blur up to 3D for the flicker target (although not inproved relative to "no blur 2"). The orientation target however cannot be located easily, with response times increasing as the level of blur increases.

7.6 Displacement and Orientation Target Changes

Given the limitation imposed by the lack of resistance of the orientation target it seemed logical to explore different target options in an attempt to improve its resistance. The strategy adopted was two-fold: first, the existing orientation target/distractor combination was altered to determine if decreasing its spatial frequency (fundamental spatial frequency of 2.14 cpd) proved sufficient to increase its resistance; second, the orientation target/distractor combination was completely redesigned, incorporating new shape combinations and decreased spatial frequencies. Figures 6.5, 6.6 and 6.7 in section 6.5.1 illustrate the changes explored. The displacement target was also altered to the same design as the flicker target – a filled white box, to determine if, as expected, such a change would improve its detectability under increased blur conditions.

7.6.1 Method

(a) Subjects

Five subjects ranging from 18 to 20 years (mean = 19 years) were tested on each of the orientation target designs and also on the reconfigured displacement task. All were deemed normal based on the criteria outlined in section 7.3 above. In addition all subjects had 6/6 uncorrected visual acuity or better in the eye tested and total refractive astigmatism was 0.25 dioptres or less.

(b) Procedure

Each subject was examined on five separate occasions, completing the test using one design only in each session. All subjects were permitted 40 practice trials and each blur condition was then tested over 40 presentations. The order of orientation task completion was varied systematically between subjects. The displacement task was the last completed by each subject. The same eye was tested in each session.

7.6.2 Results

A cursory glance at Table 7a below shows that all target types yielded similar results, with the test proving essentially impossible above 3.00D of induced blur and a significant almost linear increase in PAVS times with increasing blur.

Group Mean PAVS Response Times – Orientation Targets

Target Type	Target A	Target B	Target C	Target D
Blur Induced				
+0.50D	0.51	0.66	0.71	0.61
+1.00D	0.65	0.88	0.91	0.80
+1.50D	1.15	1.39	1.42	1.26
+2.00D	1.62	1.84	2.15	1.69
+3.00D	3.52	3.97	4.32	3.74
+4.00D	4.98	>5.00	>5.00	>5.00
+5.00D	>5.00	>5.00	>5.00	>5.00
+6.00D	>5.00	>5.00	>5.00	>5.00
+7.00D	>5.00	>5.00	>5.00	>5.00
+8.00D	>5.00	>5.00	>5.00	>5.00

Table 7a: Group mean response times for each task completed. Target A = N vs Z (reduced spatial frequency); Target B = square Vs diamond; Target C = + vs X; Target D = N vs Z (original higher spatial frequency).

Targets B and C actually proved slightly more difficult to locate than the original design, showing increased mean response times across all blur conditions. Using a modified version of the original target design with a lower fundamental spatial frequency (part of a square wave grating with a fundamental spatial frequency of 2.14 cycles per degree), appears to very slightly improve the discriminability of the target. Its susceptibility to blur though is still very much apparent.

A two-way analysis of variance with interactions reveals a highly significant effect of blur (statistics applied to results up to 3D blur) on performance ($F = 519.15$ $p < 0.001$) and also a significant effect of target type ($F = 11.672$, $p = 0.007$). Post-hoc comparisons using the Tukey test revealed a significant difference between target C and both targets A and D ($p < 0.001$ in both cases). Neither target A or B are statistically different from the original target D ($p = 0.317$ and 0.329 respectively). Target A appears therefore marginally more resistant than either B or C but not statistically better than the original design.

The results in Table 7b illustrate that a modification of the displacement target to that of the flicker target completely eliminates any possible effect of blur. Even up to 8D of simulated myopia has no effect on performance. Subjects reported that under such conditions the entire screen appears as a blurred white mass with the displacement of the target the only discriminable feature on the screen. As such localisation of the target remained easy. Two-way ANOVA with interactions reveals no effect of blur and no difference between subjects indicating that all subjects performed consistently at increasing levels of blur (blur: $F = 1.699$, $p = 0.125$; between subjects: $F = 1.978$, $p = 0.119$).

Mean PAVS Response Times - Displacement					
Subject	**A**	**B**	**C**	**D**	**E**
Blur					
+0.50D	0.47	0.49	0.43	0.51	0.59
+1.00D	0.40	0.40	0.39	0.51	0.46
+1.50D	0.39	0.41	0.39	0.42	0.48
+2.00D	0.33	0.42	0.37	0.40	0.50
+3.00D	0.38	0.47	0.36	0.41	0.39
+4.00D	0.40	0.45	0.41	0.38	0.44
+5.00D	0.41	0.40	0.41	0.46	0.53
+6.00D	0.52	0.37	0.46	0.37	0.42
+7.00D	0.43	0.39	0.44	0.48	0.40
+8.00D	0.40	0.48	0.48	0.41	0.43

Table 7b: Mean response times of each subject to a new displacement target.

7.6.3 Discussion

The spatial frequency and orientation design changes adopted here appear no more resistant to the effects of optical blur than the original high spatial frequency target design. Therefore we must postulate that an orientation target such as the one employed by this test is unsuitable for testing patients with reduced acuity. A stationary target may need to employ some different characteristic such as a luminance or colour difference to remain salient under blurred conditions. However, search appears to remain very efficient, only marginally affected by up to 1D of optical defocus. This equates to a Snellen acuity of approximately 6/12. As such, the majority of patients should be comfortably able to complete the orientation task once optically corrected.

The displacement target, as expected, becomes totally resistant to blur with the modification employed here. The lower spatial frequencies (reduced significantly from 4.3cpd to 0.54cpd) mean that the feature difference remains easily detectable with increased blur.

One of the principal benefits of the original target/distractor design is that three fundamentally different combinations are used, differing in terms of the extent and type of motion, spatial frequency and shape. As such the targets may be assumed to evaluate the sensitivity of different subsets of ganglion cells. The flicker target is already completely resistant, the displacement target is resistant to significant defocus and the orientation target resistance is largely unimproved by redesign. In the absence of a vast improvement in PAVS performance under blurred conditions for the new orientation target designs, the benefit of employing such fundamentally different stimuli possibly outweighs any minor (but not statistically significant) improvement induced by the spatial frequency reduction in the Target A orientation design. We therefore must conclude that the original target design remains the most suitable configuration for clinical use.

In subjects where best visual acuity is reduced the interpretation of the orientation results must therefore be approached with caution. The flicker and displacement tests should give some indication as to the level of performance that the subjects should potentially achieve with the orientation task. Chapter 11 shows normal performance levels for each of the three tasks, showing that response times on the orientation task are on average about 50% higher than that on flicker and displacement for normal subjects. If orientation performance falls below this then perhaps blur is contributing to the overall effect and consideration should be given to ignoring the orientation results.

CHAPTER 8

ADULT AGE EFFECTS ON PREATTENTIVE VISUAL SEARCH

8.1 SUMMARY

Background/aim: Visual search proficiency is known to decrease with age. Glaucoma, along with most clinical conditions affecting the eye is known to become more prevalent with age. As such, the application of a reaction time based test of visual search efficiency for detection of glaucoma or other ocular disorders, must take account of any such task-specific age effects to maximise the diagnostic capacity of the test.

Methods: 141 subjects, ranging in age from 16 to 85 years, were examined using flicker, motion displacement and orientation feature search tasks. Choice reaction time (CRT) test data were used to explore the extent to which any observed age effects could be attributed to psycho-motor factors, and the determination of a PAVS/CRT index provided a search performance indicator free from any such effects.

Results: The data show that most of the age effects observed can be attributed to psycho-motor factors. Increasing age has a detrimental, statistically significant effect on PAVS efficiency. The orientation task was most significantly affected. However, there is also an observed increase in choice reaction times. The ratio of PAVS/CRT index of perceptual search ability (PSA) remains relatively unaffected between age groups.

Conclusions: The results here confirm previous findings of a limited effect of age on preattentive (feature) search. The PSA index further isolates the source of this effect to psycho-motor factors i.e. parallel search mechanisms appear unaffected by age. The incorporation of a PSA index renders the test independent of the effects of age and viable for clinical application across all age groups without data manipulation for age.

8.2 Introduction

One of the more fascinating aspects of cognitive aging is the seemingly orderly relation between response times of older adults and those of younger adults, known since the 1980's (Cerella, 1985). Across disparate tasks such as identification of individual items near perceptual threshold (Cerella et al., 1982) there is typically a positive correlation between reaction time and adult age. It has also been observed that as task complexity increases, the absolute magnitude of the age differences in reaction time also increases (Salthouse & Somberg, 1982). These results have led to the formulation of a "general slowing" hypothesis, that is, the hypothesis that a single ratio of processing rates of older over younger adults can describe slowing in central cognitive processes (Cerella, 1985),

Visual search and identification tasks engage multiple forms of attentional processing, including top-down (endogenous, cognitively driven) and bottom-up (exogenous, stimulus driven) components (reviewed in chapter 2). Effective cognitive performance depends on the individual's abilities to carry out task requirements by selecting essential stimulus information, activating relevant memory representations, performing the requisite computations and ignoring or inhibiting irrelevant or interfering information. The goal of such processes is the guidance of attention to the search target. As a cognitive process, visual search is therefore subject to any such age-related cognitive performance degradation.

The origin of research on adult age differences in visual search is generally accredited to Rabbitt (1964; 1965) who compared younger and older adults in their ability to sort cards by letter identity. Rabbitt's investigations led to the conclusion that older adults have a diminished capacity to ignore irrelevant information, because older adults

appeared more disadvantaged when the number of distractors was increased. Subsequent behavioural studies of age-related cognitive change have reported a decline in attentional function in tasks involving visual search and target identification, especially when attention must be divided among multiple display items or input channels (e.g. Madden & Whiting, 2004).

Research on the development of visual search suggests that search proficiency increases from childhood to adolescence, peaks in young adulthood, and then decreases in late life. This is in accord with common views of life span cognitive development as a U-shaped, mirrored pattern of rise and fall in basic information-processing mechanisms (Hommel et al., 2004). Hannus & Allik (2002) suggest that the specific mechanisms conducting visual search are relatively mature by age seven, whereas motor abilities reach a developmental plateau by nine years of age, and general intellectual ability continues a gradual improvement. As such, it appears that child cognitive development from about six or seven years of age onwards improves attentional top-down control (more relevant for serial search) and has negligible effect on stimulus-driven performance (parallel search). Observed declines during senescence at first glance appeared to mirror the developmental gains of childhood. Early studies found significant age-related impairment of conjunction search, in contrast to largely robust feature-search performance across age groups. In feature-search conditions, as used in the present paradigm, older adults react more slowly than younger adults, especially in target-absent trials, but performance in both groups remains relatively unaffected by set-size (e.g. Plude & Doussard-Roosevelt, 1989).

More recent studies of aging effects however have revealed important refinements to the prior dichotomy between feature and conjunction search. Scialfa and Joffe (1998)

demonstrated that age effects varied as a function of target-distractor similarity. Scialfa et al. (1998) found that the search slopes of young and old adults were equally affected by manipulations of target-distractor similarity. Age deficits appear to increase with display size to a greater degree in high similarity conditions, for target-absent trials and in conjunction search. In the low similarity conditions employed in the current PAVS test, such results would suggest that age effects might be small. Kramer et al. (1996) found that young and old adults performed equivalently when conjunction search involved movement as a defining feature. Humphrey and Kramer (1997) found that both young and older adults were able to search in parallel under conjunction conditions with sufficiently differentiated features. Thus, it does not appear in all cases that feature search is age invariant, nor does it appear that conjunction search differentially penalizes older adults in all cases.

While much insight into the nature of such age deficits has been gained, the cause(s) of such effects have proved somewhat more difficult to identify with any degree of certainty. Some degree of this age-related decline is a consequence of bottom-up deficits in the sensory and neural systems supporting the transmission of the visual signal (Spear, 1993; Sandell & Peters, 2001). Other behavioural studies have revealed an additional age-related decline in top-down attentional selection (Folk & Lincourt, 1996; Watson & Maylor, 2002).

8.2.1 Non-Attentional Age Effects

While contemporary research on adult age differences in visual search has tended to ascribe obtained deficits to declines in either the spatial focussing of processing resources or the ability to divide attention across multiple inputs, others have highlighted the potential role of earlier processes in performance efficiency (Scialfa,

1990). In the elderly, pre-retinal image degradation and slower encoding results in featurally-compromised representation of spatially-extended search arrays. The older observer must therefore make a decision as to target identity or location possibly without sufficient information in an essentially reduced functional field of view.

Rabbitt (1964) acknowledged that age-related changes in spatial sensitivity (e.g. acuity, contrast sensitivity) could result in less discriminable display elements. This, essentially sensory hypothesis was initially rejected because other data (e.g. Birren & Botwinick, 1955) had demonstrated age differences in making discriminations when spatial sensitivity did not appear to be critical to task performance. Current knowledge of both age differences in sensory processes and the effects of sensory deficits on visual search now indicate that rejection of this hypothesis may have been over-hasty. Many changes in both structure and function of the visual system accompany the aging process, too many to discuss within the limits of this chapter (but summarised in Weale, 1992). The effects of parameters such as luminance, image clarity, retinal location and inter-element separation however are all important determinants of distractor effects in search and shall be addressed.

The most pronounced effect of senile miosis is a decrease in the amount of light impinging on the retina. In addition, the crystalline lens becomes less transparent with age (Said & Weale, 1961). The combined effect of senile miosis and lens changes is a significant decrease in retinal illuminance among older individuals. Therefore equiluminant stimuli do not produce equal retinal illuminance. Since recognition acuity is known to be luminance dependent, the elderly would therefore be expected to make more identification errors or to be slower to make a correct response than their younger counterparts potentially resulting in increased PAVS response times.

In many investigations of age differences in search, the stimuli create acuity demands that are inversely proportional to stimulus size. Even with appropriate optical correction, older adults do not possess the spatial resolving power of the young adult. Such losses are not confined to high spatial frequencies but contrast sensitivity effects are observed across a range of intermediate frequencies (Owsley et al., 1983). A loss in contrast sensitivity will generally yield higher error rates for briefly exposed arrays and longer latencies for correct identification trials (Schultz & Eriksen, 1978). The size of the targets used, in particular for orientation, is therefore crucial.

By their nature, visual search tasks require the presentation and identification/localisation of peripheral targets. While there is little data on the age effects on peripheral acuity, it can be safely assumed that peripheral acuity should be affected in a manner similar to the observed age-related losses of foveal spatial resolution and light sensitivity across the visual field. Experimental strategies (including that used in the present study) typically surround targets by a significant number of distractors. In the periphery, distractor effects can be more pronounced when target-distractor separation is small (Estes, 1982). The evidence suggests that such effects are sensory in nature, the result of lateral inhibition among neighbouring receptive fields or perceptive hypercolumns in the visual cortex (Levi et al., 1985). Older adults' exhibit increased lateral interference effects both in central and peripheral vision (Sloane et al., 1987).

In summary, age-related changes in the pre-retinal and neural visual system combine to reduce image clarity and energy. Since age-specific array durations or stimulus intensities are seldom employed, decreased stimulus strength will render elements within the display less discriminable. Furthermore, this effect will be more pronounced

for the peripheral targets generally used. The stimuli employed in the current test are all supra-threshold, with high contrast, high luminance, large size, large spacing between elements and a high dissimilarity between target and distractors. The sensory effects of age on thresholds might thus be expected to be less problematic in the current paradigm.

8.2.2 Attentional Age Effects

Other aspects of information processing such as cognitive speed and inhibitory efficiency play a role in determining performance level across age groups. Cognitive capabilities are affected by processing speed, and cognitive aging is associated with a general slowing of information processing (Salthouse, 1996). Older adults have been consistently shown to accumulate data less efficiently than younger counterparts (Madden & Allen, 1995). As such, increasing age can be expected to result in a general decrease in response times for feature search, and a more pronounced effect as cognitive complexity increases or when more items need to be searched serially.

Many cognitive tasks require the efficient inhibition of irrelevant information. Cognitive aging is assumed to go hand in hand with the decline of efficient inhibition (Dempster, 1992). As inhibitory difficulty increases, for example with increasing numbers of distractors or with conjunction search, then loss of inhibitory efficiency can be expected to affect performance with age.

In a response time paradigm where accuracy is emphasised, as is the case in the present study, it is also important to note the effect of age-related decision factors which result in a phenomenon known as the speed-accuracy trade off (SAT), where older adults appear to sacrifice speed to ensure accuracy (Madden & Allen, 1995).

Given unlimited time to respond, subjects would generally make few or no errors in target detection and the reaction times would not accurately reflect the decision processes involved. Subjects are therefore generally encouraged to respond as quickly as they can without sacrificing accuracy, i.e. to choose a region of response speed in which errors are relatively low but reaction times are influenced by task demands. In what is possibly an adaptation to the effects of aging, older adults appear to rely more on top-down attentional control than younger adults, helping to maintain accuracy but necessarily sacrificing speed. This possibly reflects a more cautious search strategy adopted by older adults (Hommel et al., 2004). Analysis of functional neuro-anatomical age differences in visual attention using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) reveals increased activation of frontal and parietal cortical regions in older adults for attentional control tasks compared to more occipital activation in younger adults on such tasks (Madden et al., 2006). Such reliance on frontoparietal mechanisms possibly indicates that older adults increasingly rely on additional top-down attention to support the behavioural goals, whereas younger adults make more use of bottom up information. As cortical noise increases with age (Li et al., 2001), bottom-up information may be too weak or at least judged to be an inadequate basis for a response so that top-down attentional allocation becomes more important in the elderly (although this may be less important in the supra-threshold stimuli here).

The evidence therefore confirms that older adults are less able than the young to optimise the allocation of attentional resources in some search tasks. Sensory factors also dictate that older adults would require more light, more time and more contrast to more efficiently code and encode the complex displays to which they are exposed in search tasks. The majority of data suggest that increasing task complexity has a

significant impact on search efficiency. Feature search tasks therefore are mostly affected only by cognitive processing speed so that response times although slower, remain largely unaffected by set size (Scialfa et al., 1998; Madden et al., 2004). The more complex conjunction search tasks are affected by significantly more aging effects. The aim of the current study is therefore to determine the magnitude of any age effects on the feature tasks involved and also to determine the nature of such effects through the analysis of an index of perceptual search ability (PSA).

8.3 Method

(a) *Apparatus & Stimuli*

The apparatus and stimuli used were as described in chapter 6.

(b) *Subjects*

141 subjects were examined in total. All subjects were required to have minimum visual acuity of 6/6, no significant media opacity, normal intraocular pressure, normal optic nerve head and retinal nerve fibre layer structure, an open van Herick's anterior chamber angle and free from other known ocular or systemic disease. Subjects were then classified into one of eight groups on the basis of age. Table 8a illustrates the age classifications and the number of subjects examined in each group.

(c) *Procedure*

The basic procedure was as described in section 6.3. All subjects were permitted 20 trial presentations for each target type, completing a total of 60 practice presentations. Each subject was required to be able to read a line of print on the screen from the correct fixation distance, each letter subtending half the visual angle of the test targets. Following the practice session, subjects began the test proper, firstly for the flicker

target, followed by the displacement and then finally for the orientation target, through their near optical prescription if any (modified subjectively for the fixation distance where necessary). Each single test consisted of 40 presentations of each target type.

An important component of this experimental paradigm was the completion of an additional simple reaction time (SRT) test followed by a choice reaction time (CRT) test (Figure 6.4). Section 6.32 carries a full description of both tests. Each SRT/CRT test consisted of 10 presentations. The SRT was used to identify any subjects with motor or neural response difficulties while the CRT was used to derive an index of PAVS performance modified for any such processing artifacts (increases in response time in the absence of confounding distractors), namely a perceptual search ability (PSA) index. The PSA index was thus used to isolate the true influence of age on preattentive search efficiency.

Age Grp	< 20 Yrs	20 – 29 Yrs	30 – 39 Yrs	40 – 49 Yrs	50 – 59 Yrs	60 – 69 Yrs	70 – 79 Yrs	≥ 80 Yrs
No. of Ss'	30	17	14	17	18	22	14	9
Mean Age	18.27	24.00	34.64	44.59	55.17	64.45	73.93	82.11

Table 8a: Age classifications and subject distributions

8.4 Results

Figure 8.1 shows the effects of age on (a) mean PAVS response time for a flicker target, (b) mean CRT, and (c) the mean ratio of individual PAVS/CRT values. The latter was used to provide an index of perceptual search ability (PSA) for which the influence of motor, cognitive and decision factors is minimized. It is clear that increasing age had a detrimental effect on PAVS causing a 68% increase in the group

mean reaction time from the youngest to the oldest groups. The PSA index of perceptual search ability was relatively unaffected, with a marginal decrease (-1%) in PSA from youngest to oldest.

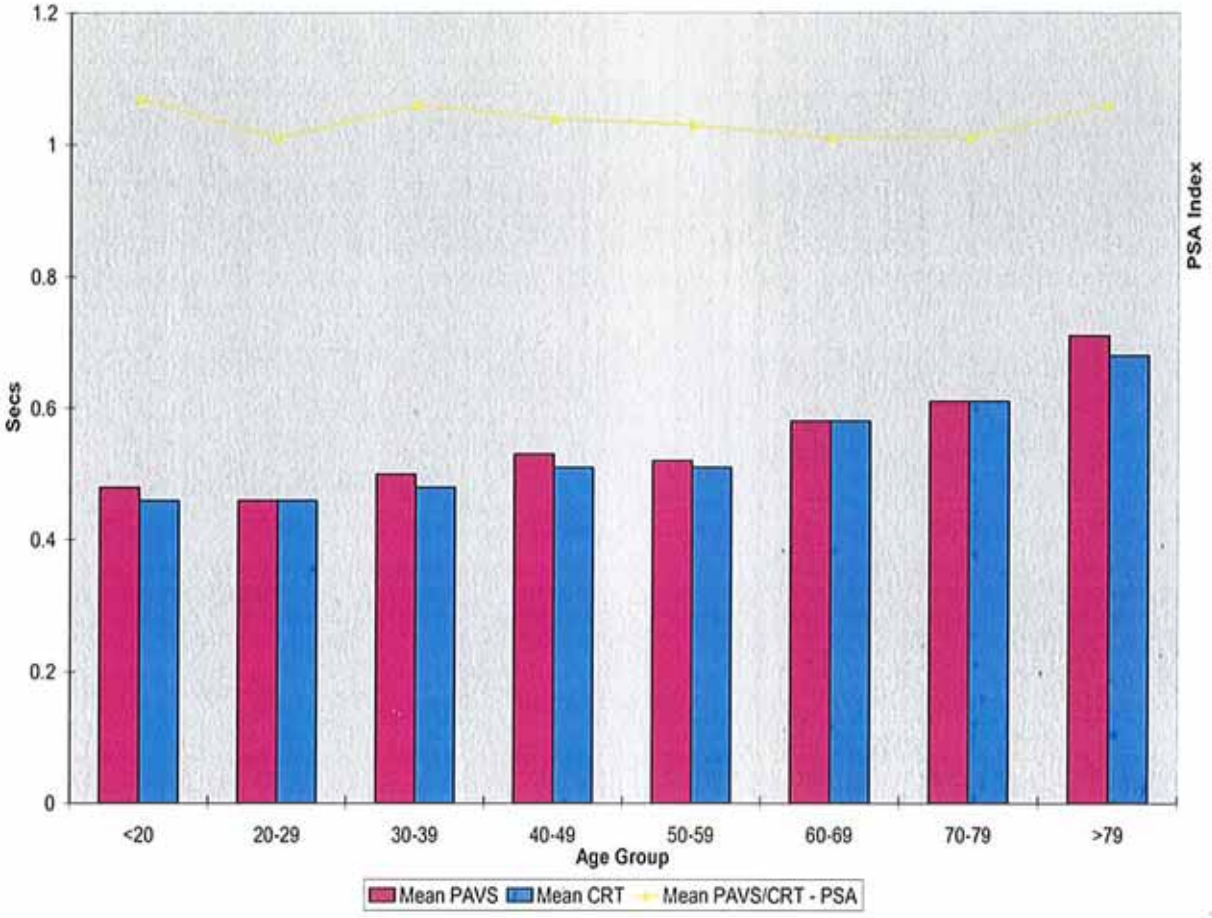


Figure 8.1: Effect of age on PAVS and PSA for flicker

Between age groups, one-way ANOVA indicated that the effect on PAVS is highly statistically significant ($F = 13.328$, $df = 7$, $P < 0.001$), but not significant for PSA ($F = 0.677$, $df = 7$, $P = 0.691$). Tukey's post-hoc analysis of the PAVS data reveals no statistically significant difference between any of the younger groups up to the 50-59 age group. The 60-69 group is statistically different from the under 20 ($p = 0.002$), the 20-29 group ($p < 0.0001$), and the over 80 group ($p = 0.001$), but not from any of the other groups. The over 80 group is statistically significantly different from all other age groups. The 70-79 group is significantly different ($p < 0.05$) from all groups except

the 60-69 group (p = 0.104). The same post-hoc test unsurprisingly reveals no significant differences between any of the groups for the PSA index.

Figure 8.2 shows the effects of age on PAVS response time for the vertically displaced target. Also shown are CRT and PSA index.

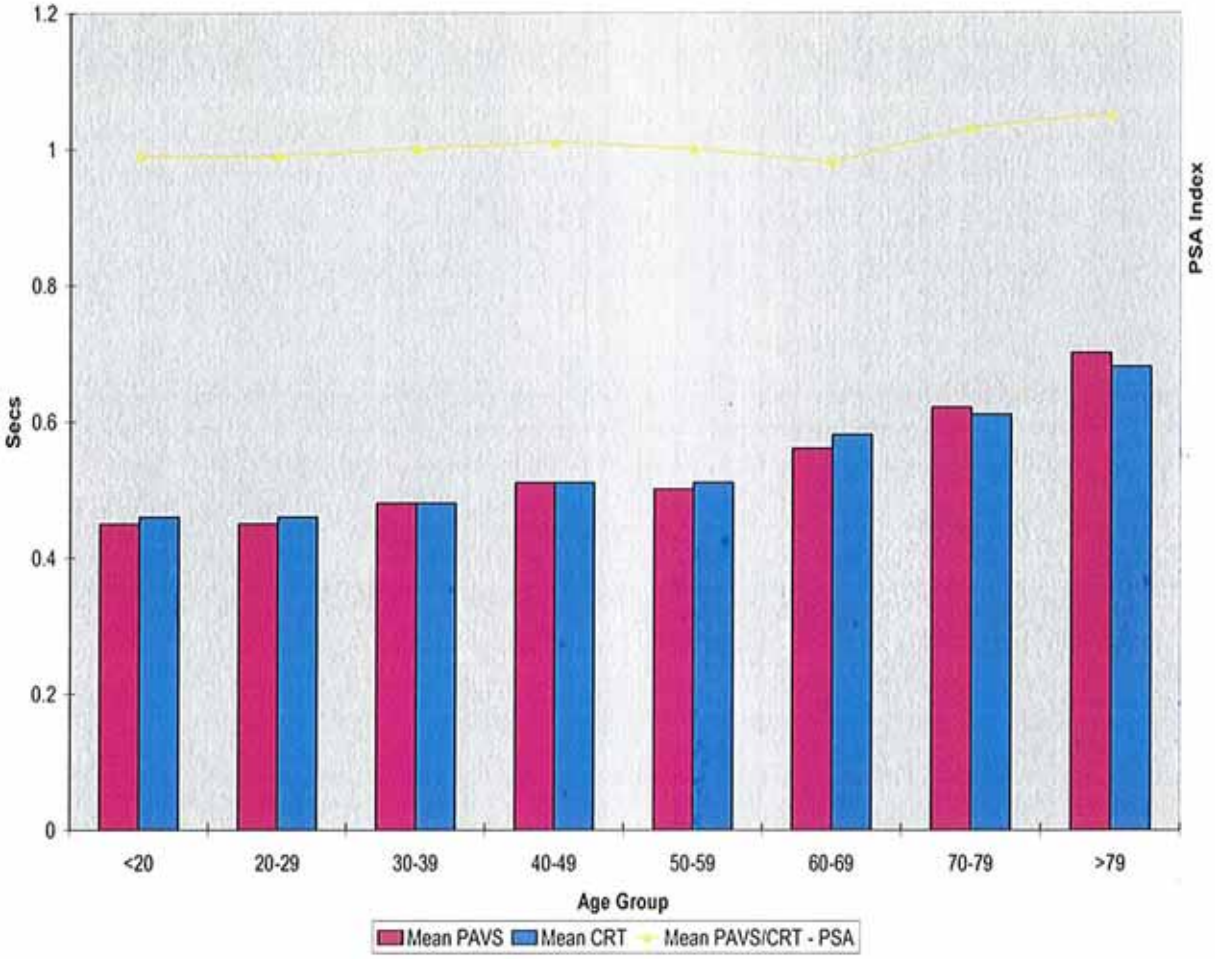


Figure 8.2: Effect of age on PAVS and PSA for motion displacement

The effects of age for this target show a similar pattern to that for the flicker target in Figure 8.1. Group mean PAVS times are increased by 65% while the effect of age on PSA is small at 6%. One-way ANOVA showed a significant effect of age on PAVS efficiency ($F = 18.218$, $df = 7$, $P < 0.001$), but no effect of age on PSA for the vertically displaced target ($F = 0.473$, $df = 7$, $P = 0.853$). Tukey's post-hoc analysis

shows no statistical significance among the five youngest groups for PAVS. The statistical difference becomes significant once again over the age of 60 ($p < 0.001$). The oldest group are again statistically less efficient at PAVS than all other groups. There is no statistical difference between any of the groups for the PSA index.

In the case of the orientation target however, the effect of age on PAVS is seen in Figure 8.3 to have been greater than for the other targets, with the result that the PSA index is more affected by age than for the other targets.

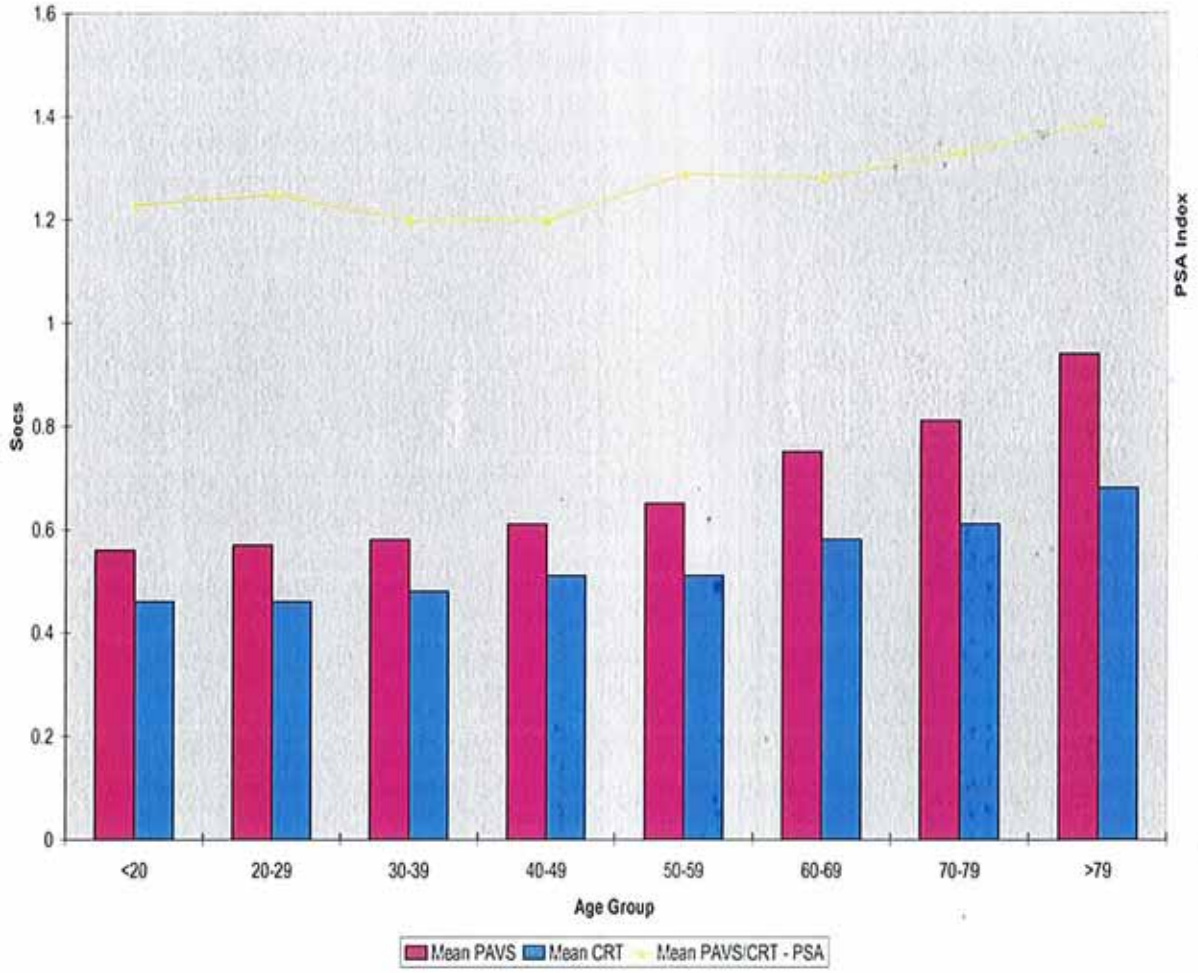


Figure 8.3: Age effects of PAVS and PSA for orientation

Group mean PAVS times are again increased by 68% while the PSA index is increased by approximately 13% from youngest to oldest. One-way ANOVA showed the effect

of age on PAVS to be significant (F = 15.964, df = 7, P < 0.0001). PSA is again statistically unaffected by age, but on this occasion the results are somewhat marginal with the significance level reaching a mere 9% (F = 1.809, df = 7, P = 0.090). Tukey's post-hoc analysis again isolates the 60-69 group as the initial source of variance in performance efficiency for PAVS, the difference being statistically significant when compared to the four youngest groups (p = 0.0001, 0.001, 0.003 & 0.021 respectively). Once more, the oldest group are statistically less efficient than all other groups at PAVS. There is no statistically significant difference between any age group's PSA.

Age Group	Flicker PSA	Flicker PAVS	Disp'ment PSA	Disp'ment PAVS	Orient'n PSA	Orient'n PAVS
<20	1.1286	0.5049s	1.0502	0.4715s	1.3046	0.5793s
20-29	1.0678	0.4847s	1.0384	0.4672s	1.3223	0.5940s
30-39	1.1624	0.5333s	1.0504	0.5043s	1.2405	0.6074s
40-49	1.0875	0.5565s	1.0399	0.5334s	1.2270	0.6309s
50-59	1.0873	0.5535s	1.0654	0.5225s	1.4081	0.7006s
60-69	1.0620	0.6201s	1.0479	0.6199s	1.3636	0.8402s
70-79	1.0633	0.6781s	1.0773	0.6757s	1.4562	0.9192s
≥80	1.123	0.8423s	1.1700	0.7750s	1.4470	1.0925s

Table 8b: 97.5% confidence interval for mean (upper bound only) of PSA and PAVS for each task

Table 8b outlines the 97.5% confidence intervals (upper-bound only) for each age group for both PAVS and PSA. As the PSA index is more robust this perhaps provides the best indication of target specific expected upper limit of normal values

The observed upper limit of normal PSA values are approximately 1.17 for both flicker and displacement and up to 1.46 for orientation.

8.5 Discussion

Age-related selective attention deficits have been demonstrated in studies showing age increments in target identification time and error rate as a function of increasing non-target information in visual search tasks (e.g. Plude & Hoyer, 1981). Most theories of visual search such as feature integration and guided search suggest a two-stage model of visual processing that comprises an initial stage of feature extraction and a subsequent stage of feature integration. In the feature-extraction stage, feature detectors "operate early, automatically and in parallel across the visual field" (Treisman & Gelade, 1980), while in the integration stage, extracted features are conjoined through serial focal attention to represent the complex components of the visual field.

In relation to age deficits in visual search the primary question concerns the locus of age differences in the sequence of visual information processing. Search theories suggest that focal attention and serial processing are required in visual search only when non-target items combine to form patterns that are confusable with the target. When the non-target items do not contain the features of the target, target identification can be completed using parallel processes alone (as in the present study). Thus, young adults exhibit performance that is unconstrained by attention under feature search but not in conjunction search. Investigations into the nature of age-related search deficits have confirmed that older adults also produce zero slopes in reaction time or error rates with increasing display size, indicating that parallel search is relatively unaffected by age (Plude & Doussard-Roosevelt, 1989).

The current paradigm differs from conventional psychological strategies designed to elucidate the nature of visual search in that the critical factor is response time for a fixed display size. Age effects will therefore manifest as increased response time between age groups rather than between display sizes. As such, the current paradigm cannot isolate true age effects on parallel search capabilities without factoring the variable influence of individual psycho-motor and sensory factors. The use of a choice reaction time test in association with the PAVS test however solves this dilemma. The CRT provides a baseline response time which will be degraded by all those factors, sensory, motor and neural that can influence a response time paradigm. The perceptual search ability (PSA) index thus isolates the individuals' parallel search capabilities independent of attentional and sensory deficits.

The current PAVS test employs targets fitting the feature search criterion, differing significantly from surrounding distractors on the basis of orientation, flicker and motion displacement and all being elementary features capable of capturing attention in parallel (Julesz, 1971; Sagi & Julesz, 1985a; Driver & McLeod, 1992).

The data presented here support the expected finding of an adverse effect of age on PAVS response times. Although the largely parvo mediated orientation task yields consistently increased response times relative to the predominantly magno mediated motion and flicker tasks, the increases with age are remarkably similar at 68%, 65% and 68% for flicker, displacement and orientation respectively. Surprisingly, the group-mean response times are fastest for the 20-29 group for both the flicker and displacement tasks. As would be expected, the under-20 group performs best on the orientation task. Across all target types, the age effects are minimal up to age 59. The increase in PAVS response times is approximately 8%, 11% and 17% for the flicker,

displacement and orientation tasks respectively by age 59. The majority of the age deficit appears in groups older than this. This finding is in general agreement with the findings of Zacks & Zacks (1993). Acknowledging the potential for error when using a RT strategy to analyse the effect of age on visual search through the influence of non-search deficits, they devised a forced-choice judgment with limited duration stimuli method to minimize such non-search effects. Their results confirm a quantitative cognitive change in aging as a slowing of visual search rate. In their data, the rate of slowing appears to increase dramatically after the age of 65.

Once the PAVS data is modified using the CRT times to create a perceptual search ability index, the observed age deficits disappear across each target type. For the flicker target the disappearance is complete and in fact the group with the best PSA score was the 60-69 group, previously identified as the source of variance in PAVS efficiency. The effect is mirrored for the displacement target. PSA remains high across all age groups and once again the 60-69 group achieves the best PSA score. On the orientation task, the PSA scores are lower in general than for the other tasks. This perhaps reflects the nature of what more resembles an acuity task. As such it is more likely coded by the more sustained, slower-conducting parvo system. The age effect, while non-significant, is slightly larger also than for the other tasks, perhaps a consequence of sensory factor effects on discriminability of the target and distractors (despite good high-contrast spatial acuity). The confidence values given in Table 8b provide a useful guide as to the expected level of performance in a normal population. While the sample sizes are probably too small to provide a reference normal database as yet, it can be seen that once the PAVS time is increased to the 97.5% confidence interval limit, it reaches about 20% above the mean CRT time for flicker and displacement, and 40% for orientation, above this the result becomes suspicious. This

however does not provide concrete evidence of abnormality. The global picture needs to be examined in each case.

For example, one 19 year old subject recorded the highest PSA score in that group of 1.41, 1.33 and 1.49 for flicker, displacement and orientation respectively. At first glance these all appear abnormally elevated. Closer inspection however reveals that this subject's PAVS times were still quite fast at 0.55s, 0.52s and 0.58s respectively, which are at the slower end of the scale but not unusually so. Of the 30 subjects, this individual recorded the fourth fastest CRT time at 0.39s. It is thus more likely an artifactual rather than truly abnormal finding in this case. Once a high PSA score is obtained, it is clear that the raw PAVS and CRT data should be inspected to confirm the source of the increase.

Despite differences in the experimental design, the results here appear to support the conclusions of most of the available gerontological data. There appears to be a general slowing of visual search performance but this effect seems to be isolated to non-parallel sensory and/or attentional deficits.

Combining the PAVS and CRT creates a PSA index that renders the current test independent of the effects of age and therefore suitable for use in the detection of clinical conditions such as glaucoma that may be more prevalent in older age groups. Age alone will therefore not factor in accurate diagnosis of such conditions once PSA scores are used as the critical performance indicator.

CHAPTER 9

TASK-SPECIFIC PERCEPTUAL LEARNING EFFECTS ON PREATTENTIVE VISUAL SEARCH EFFICIENCY

9.1 SUMMARY

Background/aim: The performance of adult humans in simple visual tasks improves dramatically with practice. As such, the clinical application of a visual search based test must provide for sufficient practice to prevent learning effects from confounding the results obtained. The current study has been designed to determine the nature, timeframe, duration and specificity of the perceptual learning effects for each of the three search tasks used to assess PAVS efficiency here.

Methods: Perceptual learning effects were explored using two separate distinct strategies (see Paradigm 1 & 2 below). Subject performance was tracked from the initial target presentation to determine the amount of practice required before the effect reached a plateau. Subjects were tracked longitudinally to determine if the learning effects were sustained, and switched to a different target or the other eye to ascertain if learning effects transferred.

Results: The results suggest a fast learning process across all tasks which persists for a minimum of six months and is not specific for the target or the eye trained.

Conclusions: The nature of the search tasks employed is such that the observed learning effects are rapidly saturating, non-specific and sustained. Only a small number of practice presentations for each target type would be required prior to test application which has obvious merit for use of the PAVS test in a clinical environment as testing is usually performed in conditions where time is limited.

9.2 Introduction

The adult visual system retains a surprising degree of plasticity evident in the ability of subjects to improve substantially and rapidly on a wide range of visual tasks (Ahissar & Hochstein, 1996). Such improvement in the ability to get information from the environment as a result of practice with the environment is called "perceptual learning" (Gibson, 1953). Performance in visual perceptual tasks therefore appears to be restricted significantly by limitations in the ability of the visual cortex to analyse adequately the information supplied by the eyes, and not just by absolute limitations of the visual system at least initially (Fahle & Henke-Fahle, 1996). It is therefore the inaccessibility of task-relevant information rather than the absence of such information within neural representations that limits naïve performance. The cognitive effects involved in perceptual learning have been observed in visual search (e.g. Sireteanu & Rettenbach, 1995), attentional processing (Ahissar & Hochstein, 1993 & 1997) and also in relatively simple tasks such as vernier and resolution acuity (Beard et al., 1995).

In the earlier literature, the perceptual learning phenomenon tended to be defined by the behavioural characteristics and manner in which it was induced, rather than by its underlying neural mechanisms. The majority of early data, in particular learning specificity findings, suggest that learning could be accounted for in terms of the tuning properties of neurons at the level of V1 (e.g. Saarinen & Levi, 1995), but there is now accumulating evidence that higher-level cognitive processes are involved. Indeed Ahissar and Hochstein (2004) have proposed a Reverse Hierarchy Theory as a unifying concept that links behavioural findings of visual learning with physiological and anatomical data. Essentially it asserts that "learning is a top-down guided process, which begins at high-level areas of the visual system, and when these do not suffice,

progresses backwards to the input levels, which have a better signal-to-noise ratio". Figures 9.1 and 9.2 below give an example of perceptual learning for pattern discrimination in action. The nature of perceptual learning can be described (at least partly) in terms of its time-course, specificity, and neural mechanisms.

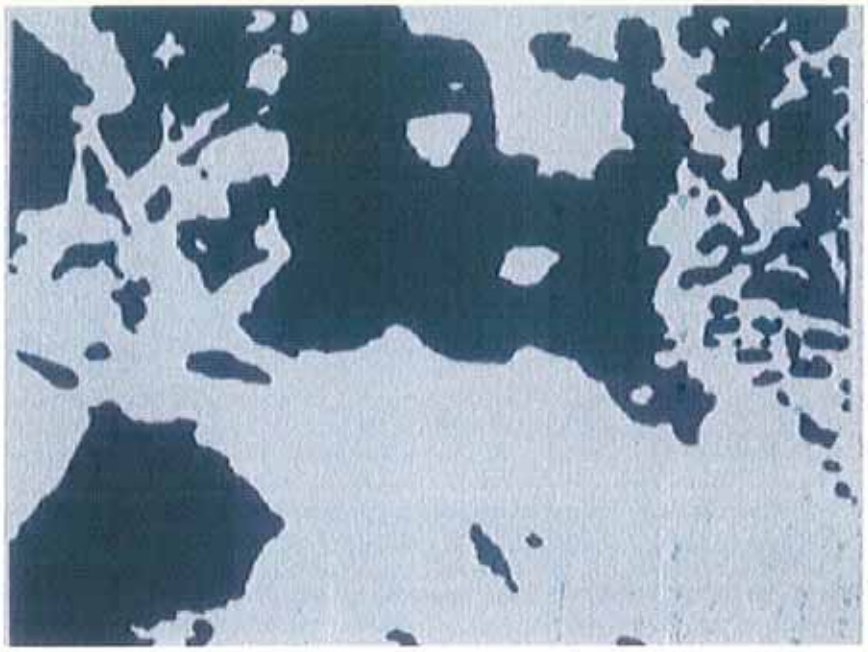


Figure 9.1: The figure typically appears as a series of black and grey regions, without further meaning. Considerable inspection or a glance at Figure 9.2 below generally allows the perceptual system to "learn" what cues to use to extract the figure. (from Ahissar & Hochstein, 2004)

Figure 9.2: A hint for "understanding" the image in Figure 9.1. A few lines draw attention to those aspects that are essential for perceiving a bearded figure. Now return to Figure 9.1 to see how this "clue" has affected your perceptual system. (from Ahissar & Hochstein, 2004)

9.2.1 Perceptual Learning Time-Course

Karni and Sagi (1993) produced some interesting and controversial initial observations on the time-course of perceptual learning on a texture segregation task. Their results show relatively slow improvement over a time period of four to five days. Except for a fast, rapidly saturating improvement early in the first practice session for suprathreshold stimuli among naïve observers, performance remained stable within sessions. In the eight hours after practice no learning was observed, but large improvements occurred thereafter, implying an incubation period in which changes induced by repetitive performance of the task were observed. Interruption of REM sleep inhibited learning consolidation. Importantly, learning effects were retained for a minimum of 2-3 years suggesting that some types of perceptual experience trigger permanent neural changes in early processing stages of the adult visual system.

Sireteanu and Rettenbach (1995) confirmed the persistence of the learning effect for texture segregation and visual search. However they reported significantly different findings with regard to the time-course. A continuous improvement occurred within sessions without a discontinuity between sessions. They also contend that initially serial tasks can become parallel with practice suggesting that parallel and serial processes are indeed extremes of a continuum as suggested by Duncan and Humphreys (1989). This would also suggest that learning is more complex than initially thought, that learning can occur at different places in the human brain depending on what is being learned. Ellison and Walsh (1998) again found learning effects to be fast and enduring with both feature and conjunction arrays. There is general consensus that the rate of learning is task specific and relates to the type and complexity of the task (Ahissar & Hochstein, 1997). Learning on easy tasks where the subject is allowed long processing times improves performance rapidly and may even serve to guide learning in more difficult tasks.

9.2.2 Specificity of Learning

The specificity of perceptual learning has proved more difficult to fully describe. Fiorentini and Berardi (1980) describe practice effects in tasks involving phase discrimination and found learning to be specific for orientation, spatial frequency and visual field location (hemifield). Karni and Sagi (1991) found learning to be specific for the visual field quadrant, background orientation and the eye used. As such it was initially suggested that learning might occur early in the central visual pathway, perhaps as early as the orientation-specific simple cells in the primary cortex (Poggio et al., 1992). Conversely however, Ellison and Walsh (1998) report substantial transfer from serial to pop-out searches but limited reverse effects. Sireteanu and Rettenbach (1995) report that learning in visual search is far less specific than learning of visual

discriminations and hyperacuity, indicating that it may occur at another level in the central visual pathway. They found that both visual search and texture segregation tasks undergo rapid perceptual learning that is not specific for the task involved or for the trained eye, undergoing complete interocular transfer. This lack of specificity may also suggest that the observed learning effect may not be an improvement in the perception of a particular 'feature' but perhaps reflects an improved search strategy.

9.2.3 Locus of Learning Effects

The reported high specificity of learning in visual discrimination and hyperacuity tasks combined with the lack of specificity in visual search suggest that it might be difficult to pinpoint the exact location of this process in the central visual pathway. Discrimination of orientation, of complex gratings, of random-dot stereograms or of vernier offsets are very likely processed in different brain regions and learning may well occur in these disparate regions. The specificity of learning on certain tasks suggests low-level learning where monocularity and the retinotopic organisation of the visual input is still retained and where different orientations are processed separately. Cortical potentials evoked by displacement of vernier lines show significantly shorter latencies and larger amplitudes after training than before and suggest that some change does occur very early during cortical processing (Fahle, 1994). According to Reverse Hierarchy Theory learning in higher cortical areas should occur faster than in lower areas. Evidence from single neuron and fMRI studies suggests that rapid long-term learning relates to modifications at higher-level cortical areas such as the inferotemporal (IT) cortex (Ahissar & Hochstein, 2004).

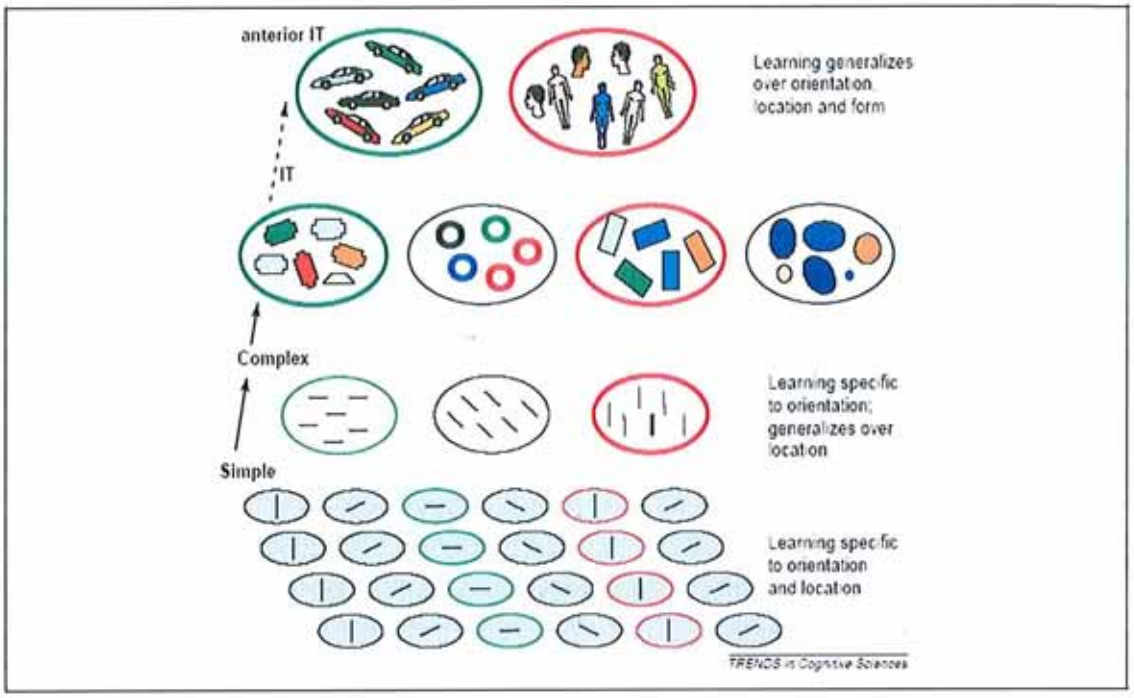


Figure 9.3: A hierarchy of cortical areas progressively processes visual information, first representing object features, for example a simple cell responding to a certain orientation. Shapes etc are represented in higher cortical areas e.g. IT. If learning modifications occur in finely tuned units at lower level areas only, these effects will be specific and not transfer to other tasks. If modifications occur in higher, more broadly tuned cortical areas then learning will transfer to new stimulus conditions (from Ahissar & Hochstein, 2004)

Such effects are consistent with rapid non-specific learning effects in visual search mediated by higher cortical areas and more specific learning effects isolated to earlier processes outlined in the Reverse Hierarchy Theory in Figure 9.3.

Psychophysical and electrophysiological studies therefore provide evidence for plasticity of primary sensory areas. Perceptual learning seems to have two major components, one fast and one slow. The fast component (occurring during the practice session) seems to affect higher level processing (above the site of binocular

integration), and probably involves top-down processes, improving the link between task-dependent units and sensory units while selecting optimal sensory units for the task. Once these links become efficient, the task becomes automatic and performance is limited by sensory architecture alone. The slow component (occurring between sessions and aided by REM sleep) seems to follow the fast one and involves low-level processes (monocular) within primary sensory areas (Ahissar & Hochstein, 1996).

The following experimental paradigms have been designed to determine the precise task-specific time-course, duration and the degree of interocular and inter-task transfer of learning. This should elucidate the length of the practice session that will be required in the clinical application of the test.

PARADIGM 1

9.3 Method

(a) *Apparatus & Stimuli*

The apparatus and stimuli used were as described in chapter 6.

(b) *Subjects*

The same 17 subjects as described in section 7.3 were used to make the initial investigation into the effects of perceptual learning.

(c) *Procedure*

The basic procedure was as described in section 6.3 with some subtle variations. Each subject's refractive and ocular health status was examined as described in section 7.3. Each subject was required to wear their optical correction and be able to read a line of print on the screen from the correct fixation distance, each letter subtending half the

visual angle of the test targets. The subject began the test proper through their near optical prescription if any (modified subjectively for the fixation distance where necessary). Each single test consisted of 40 presentations of each target type. A simple and choice reaction time test was also completed by each subject, with 10 presentations in each case.

This experiment is a continuation of experiment 1 as outlined in chapter 7. All subjects initially underwent 240 practice trials. This was followed by 120 presentations through the distance Rx, followed by 3 sets of 120 trials under blurred conditions. Finally the experiment was repeated with an additional 120 presentations through the distance Rx again. The results of the initial distance Rx test were compared to the results for the final distance Rx test to determine whether any improvement in performance had occurred after the initial practice session. The null hypothesis here is that, after an initial training period, further testing causes no change in response time due to learning or fatigue, i.e. the mean value of "no blur 1" = mean of "no blur 2" so that 240 presentations are sufficient to "train" a subject prior to data collection.
In this experiment, "no blur 1" as in chapter 7, represents the initial test with corrected acuity and "no blur 2" represents the final corrected acuity test.

9.4 Results

Figure 9.4 illustrates that for each target, group mean results for "no blur 2" are slightly faster than those recorded for "no blur 1". Only on the flicker test is there an apparent substantial improvement in response times from "no blur 1" to "no blur 2". Figure 9.4 demonstrates this: there is very little difference between the mean response times for no blur 1 and no blur 2 on either displacement or orientation tasks. Before proper statistical analysis, this would still suggest the absence of a learning effect.

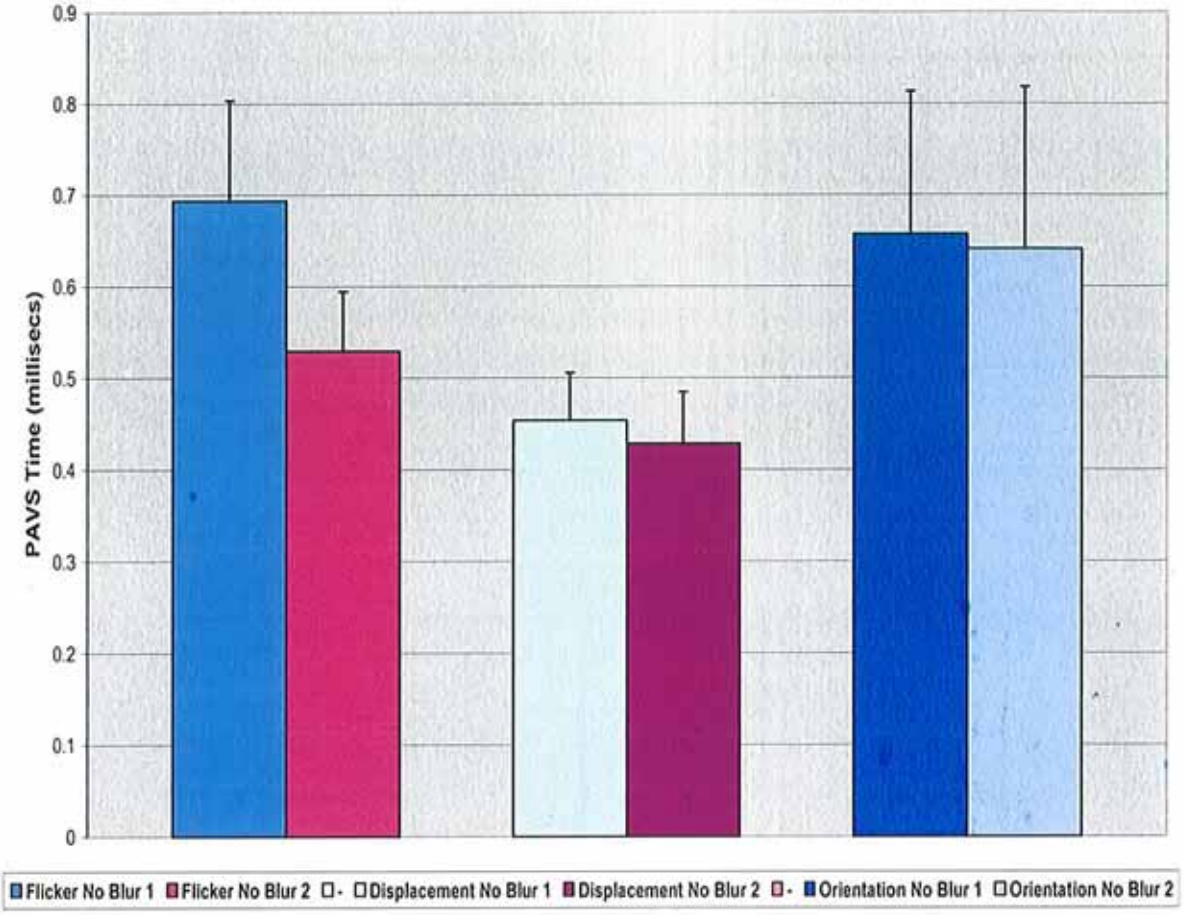


Figure 9.4: Group mean response times (+ st. dev. error bars) for no blur 1 and no blur 2 conditions across each target type

All subjects recorded faster search times for no blur 2 than no blur 1 for the flicker target. 10 subjects recorded faster times for no blur 2 using the displacement target, while 2 others had equal times for both conditions, with 5 subjects faster during the no blur 1 test. 10 subjects were again faster for no blur 2 on the orientation task with 1 subject having equal times for both and 6 subjects faster for no blur 1. Therefore, although the mean data results show on average faster response times for the no blur 2 condition, 41% of subjects actually performed better or equal to the no blur 2 results on the no blur 1 condition, for both orientation and oscillation tests.

Figures 7.1 and 7.2 show that for the flicker target there is a slight improvement in mean response times for no blur 2 over the initial no blur 1 test. The apparent

improvement is statistically significant (paired t-test: t=3.773, p =0.02). Note that the "no blur 1" condition with flickering targets was the very first test carried out by the patients following the trial period and therefore performance may have suffered slightly from various possible effects such as cautious initial responses. Thus when a paired t-test was carried out between "myopia 3D", which was the very next test carried out, and the final test ("no blur 2"), no significant difference was found (p=0.266). Randomisation of test presentation order would have been preferable but unfortunately was not possible due to software limitations in the current test design.

Figure 9.4 shows that PAVS response times for motion displacement targets are almost identical for the two distance tests "no blur 1" (mean for all subjects 0.453s, st.dev = 0.051) and "no blur 2" (mean = 0.428s, st.dev = 0.056) but the difference (surprisingly) is statistically significant (paired t test, t =2.317, p= 0.032). However, the difference between the means is only 25 milliseconds, which may have no practical significance.

Figure 9.4 also shows little improvement in performance between initial and final tests for orientation targets, and the difference is not statistically significant (paired t test, t = 0.507, p = 0.619).

9.5 Discussion

The data presented here were all recorded after two complete practice runs through the test protocol. During this practice protocol, a learning effect may well have taken place. The data presented suggest that after 240 practice presentations a learning plateau had already been reached for the displacement and orientation task. The flicker test however shows some degree of improved performance between the initial and

final test sessions. Based on extensive observations however, we would contend that this improvement is not a consequence of further perceptual learning but rather an artifact of the experimental design. Subjects were informed that the test proper was about to commence after the 240 practice trials. With hindsight, it was perhaps a mistake to differentiate the two sections. Being aware that the test proper was about to begin, subjects perhaps adopted a more cautious response strategy initially reflected in the increased response times for the flicker no blur 1 condition. This was the very first data set completed after the practice session. Analysis of variance in the remaining flicker data would tend to support such a conclusion. However, in the present study we did not collect data in such a way as to elucidate the exact timeframe of the perceptual learning effect (this is the subject of the data collected in Paradigm 2).

PARADIGM 2

Following the results of the initial exploration of perceptual learning, a new strategy was devised to more fully describe the task specific perceptual learning effects of the current PAVS test.

9.6 Method

(a) *Apparatus & Stimuli*

The apparatus and stimuli used were as described in chapter 6.

(b) *Subjects*

Four subjects were examined in total, three younger observers (aged 22, 24 and 23 respectively), and one older observer (age 68). All subjects were naïve to typical visual search tasks. All subjects had minimum visual acuity of 6/6 in the eye tested and were deemed free of ocular disease by examination as described elsewhere and systemic

disease by self report. Each subject was assigned to and trained on one of the three tasks alone during the primary sessions.

(c) *Procedure*

The basic procedures were as described in section 9.3 above. The key difference however in this experimental paradigm was the absence of any period of practice prior to commencing the test. Subjects were thoroughly instructed as to the nature and requirements of each task. One eye was occluded with a black patch (the test was carried out on the eye with the better corrected v.a or the right eye if no discernible difference in v.a was detected). Subjects were randomly assigned to a single target type, flicker, motion displacement or orientation, and initially completed all presentations for that task alone.

Each subject completed five test sessions, labelled session 1, session 2, session 3, session 4 and switch session. In each session subjects performed three sets of 40 presentations, for a total of 120 presentations at a single session. Sessions 1, 2 and 3 all took place within an initial two-week period with each subject completing a total of 360 presentations in this time. The switch session was completed in the third week, subjects were given a further 120 presentations to test for transfer of learning. The older observer was assessed with the same target as that initially used, but using the previously occluded eye, while the remainder were assessed using the same eye for a different task. Session 4 was a final 120-presentation assessment and took place approximately six months after completion of the initial test to determine whether any learning effects persisted.

9.7 Results

PAVS efficiency as a function of the $\log_{10}$ of the number of presentations of the flicker target is shown in Figure 9.5. The improvement in performance visibly saturates after between twenty to twenty-five presentations, reaching a mean response time of 384msecs, which is below the fastest session mean of 401msecs in session 2. The mean response times of small groups of responses more clearly illustrates the learning curve.

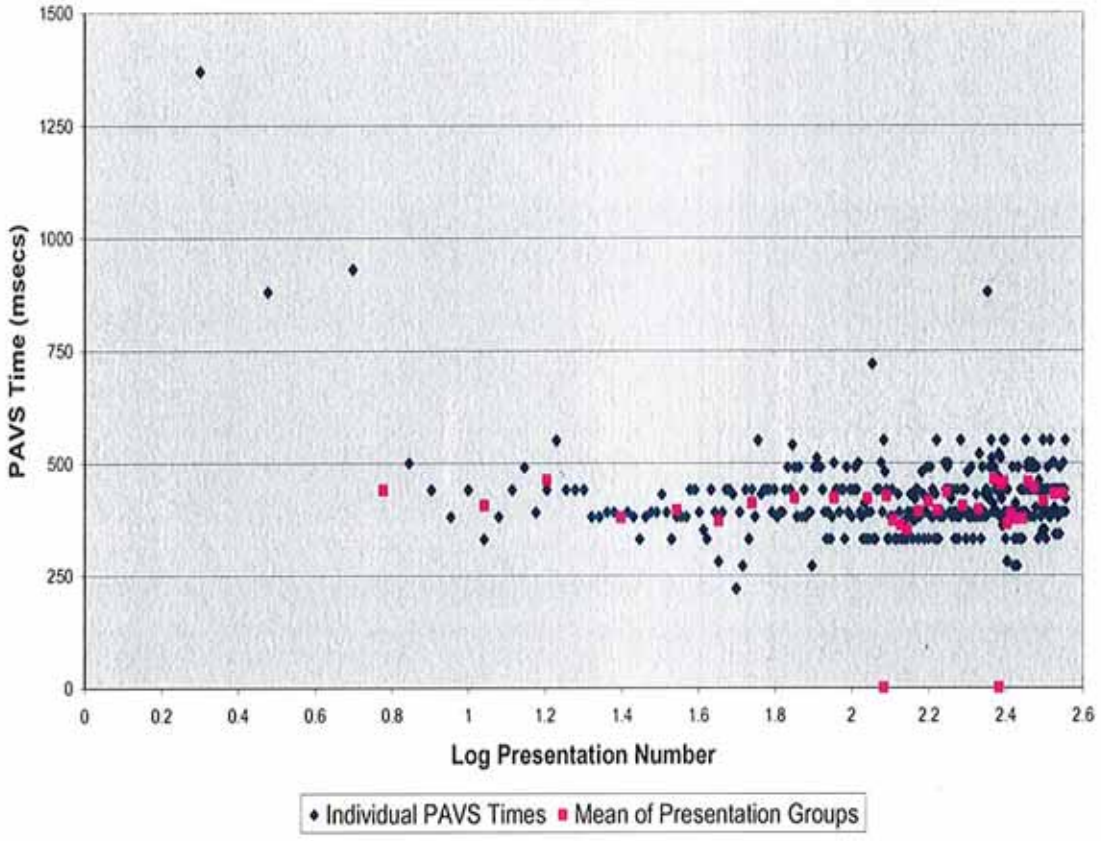


Figure 9.5: Learning curve during 360 presentations for the flicker target with superimposed mean response times of groups of presentations more clearly illustrating the learning curve plateau

Session times (displayed as means of groups of presentations within each session) are plotted in Figure 9.6. These confirm the rapidly saturating learning effect. Furthermore, the effect is maintained although there is a minor visible performance

improvement in the first few trials of each session. Friedman's test for variance in performance between sessions indicates no significant difference between the groups, most likely because the learning effect in session 1 was so rapid (chi-square = 4.107, df = 3, F = 1.373, P = 0.251).

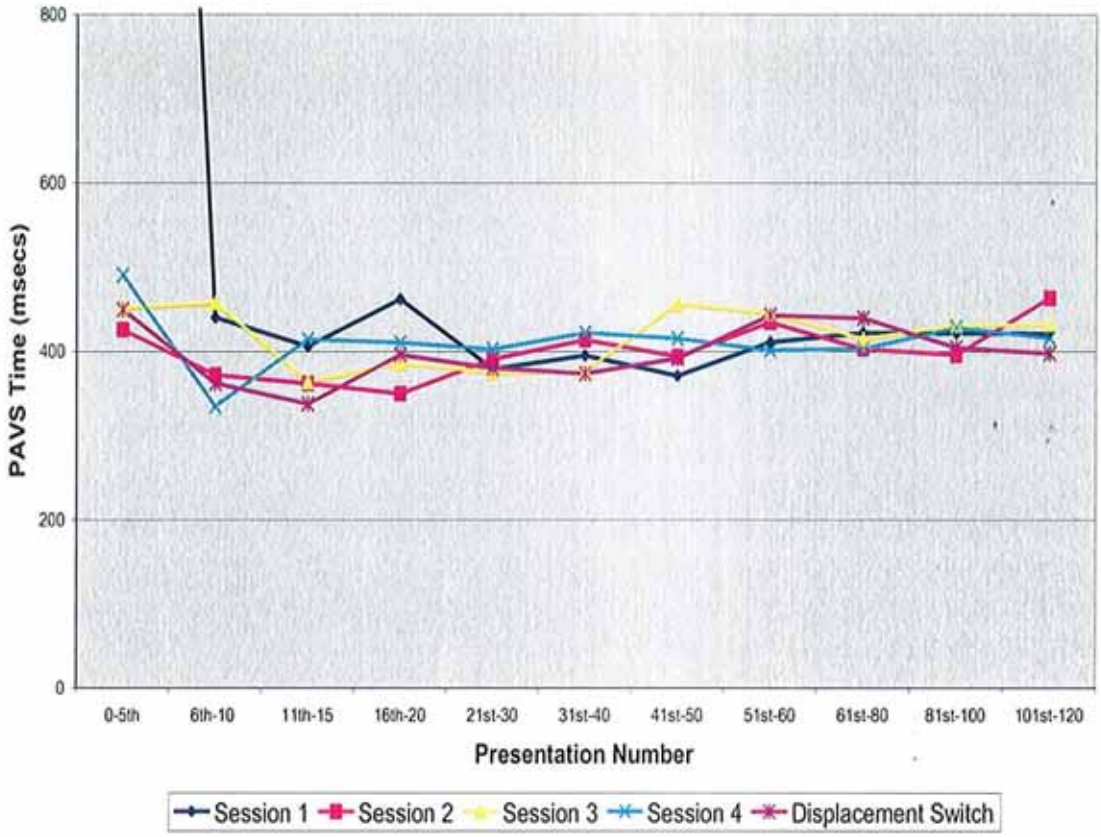


Figure 9.6: PAVS performance across sessions for flicker and transfer to displacement

Table 9a charts the linear regression analysis, which confirms that no improvement in either slope or intercept occurs after session 1. The positive slope in session 2 probably reflects a marginally increased response time in the final 20 presentations of that session possibly as a result of fatigue.

Session	Slope	Y Intercept
1	~ 0.00	400msecs
2	0.294	372.21msecs
3	~ 0.00	440msecs
4	~ 0.00	410msecs

Table 9a: Learning slopes and intercepts for each session on the flicker task

Figure 9.7 shows a flat performance curve (save for two slightly increased PAVS times at test commencement) which, when compared to the curve for displacement with no prior training (Figure 9.11) clearly illustrates that learning has transferred from the flicker task to displacement. Linear regression produces a flat slope (<0.52) and y intercept of 390msecs similar to the most efficient session in the observer trained on displacement.

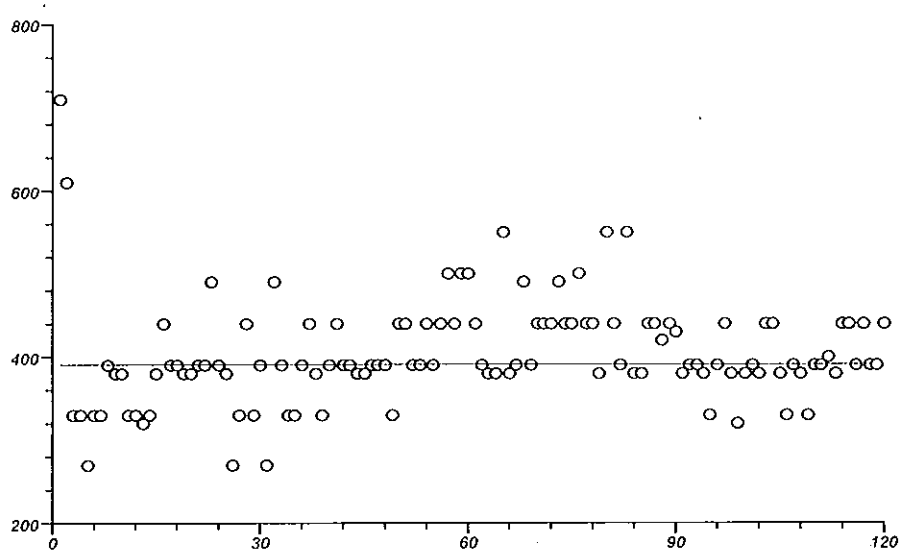


Figure 9.7: Non-parametric linear regression plot of PAVS performance following transfer to the displacement task. (Presentation Number (x axis) vs. PAVS time in milliseconds (y axis))

Figure 9.8 shows the perceptual learning curve for the orientation task. In this case the leaning plateau is shifted to the right indicating an extended learning timeframe compared to flicker or displacement (Figures 9.5 + 9.11).

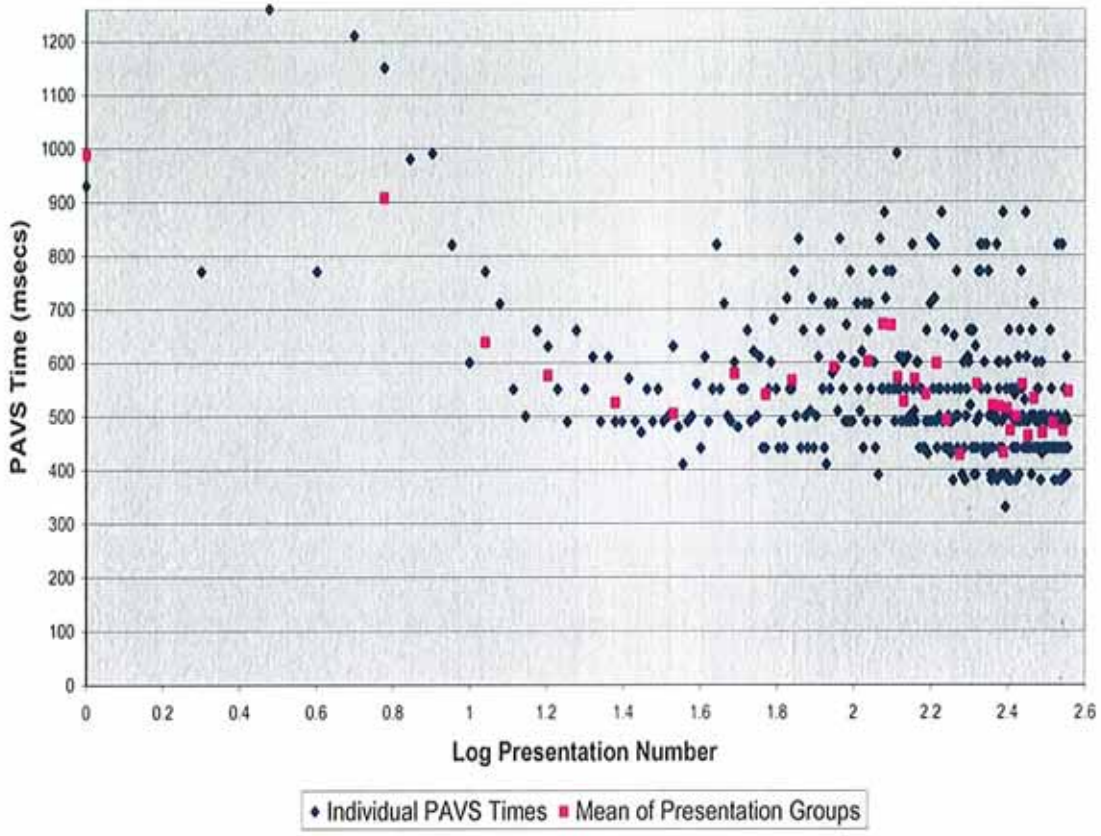


Figure 9.8: Learning curve during 360 presentations for the orientation target and with superimposed mean response times of groups of presentations to reduce the visual impact of individual variability effects.

In this case, the learning curve plateaus after approximately 40 presentations. The lowest group mean of 493msecs obtained in session 3 is reached by the 35th to 40th group mean at 488msecs.

Session times are plotted in Figure 9.9. The effect is again maintained between sessions, again with a minor improvement in the first few trials of each session.

Friedman's test for variance in performance indicates a significant difference between sessions (chi-square = 41.923, df = 3, F = 15.684, $P < 0.0001$).

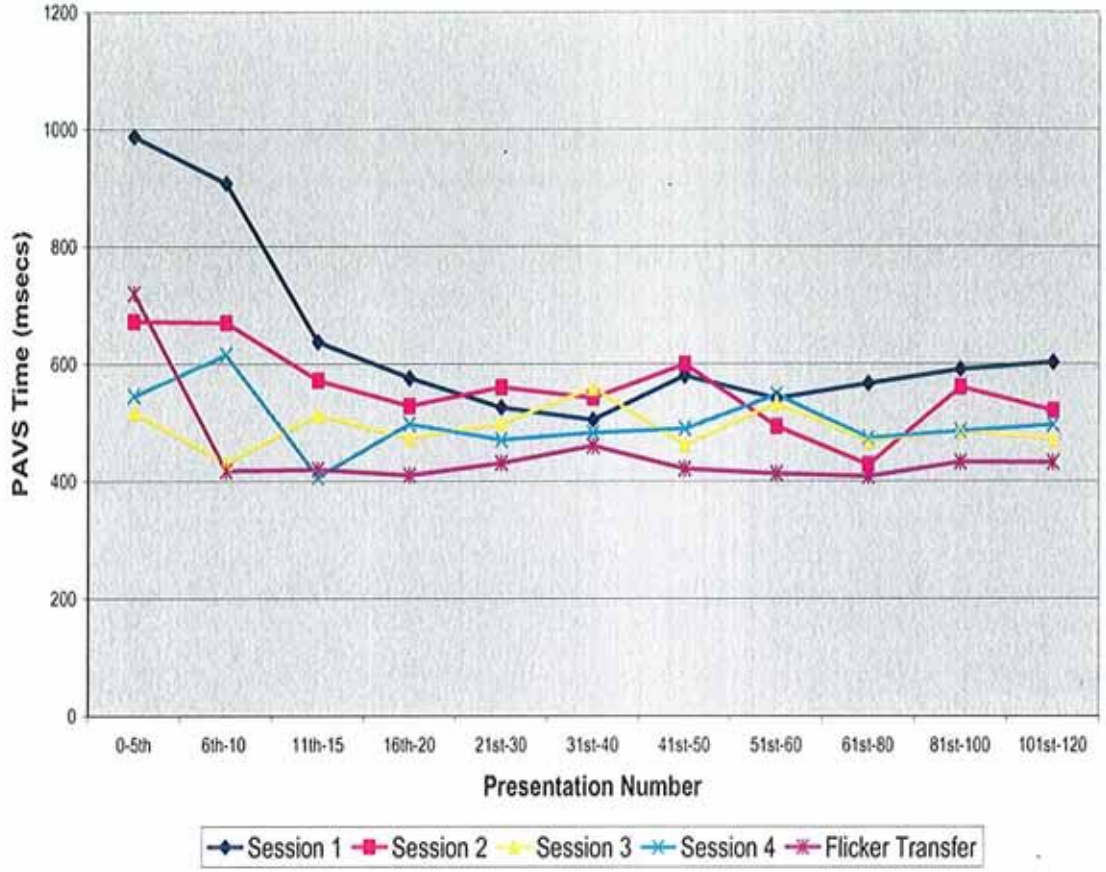


Figure 9.9: PAVS performance across sessions for orientation and flicker transfer

The principal source of variance is the initial two sessions, which are statistically significantly different to all other paired sessions ($p < 0.05$ for all pairs). The final two sessions show no statistical difference from each other (Conover paired comparisons: $p = 0.383$). The rapid saturation possibly requires further presentations before it is consolidated in sessions 3 and 4.

The apparent increased PAVS efficiency after session 2 is confirmed by the regression slope and intercept improvements in session 3 and 4 outlined in Table 9b.

Session	Slope	Y Intercept
1	-0.169	560.25msecs
2	-0.667	555.33msecs
3	~ 0.00	440msecs
4	~ 0.00	490msecs

Table 9b: Learning slopes and intercepts for each session on the orientation task

Following transfer to the flicker task, the zero performance slope confirms transfer of learning to flicker (Figure 9.10). Linear regression analysis produces a zero slope (0.00) and a y intercept of 390msecs indicating highly efficient performance immediately (save for one initial outlier) following transfer to flicker.

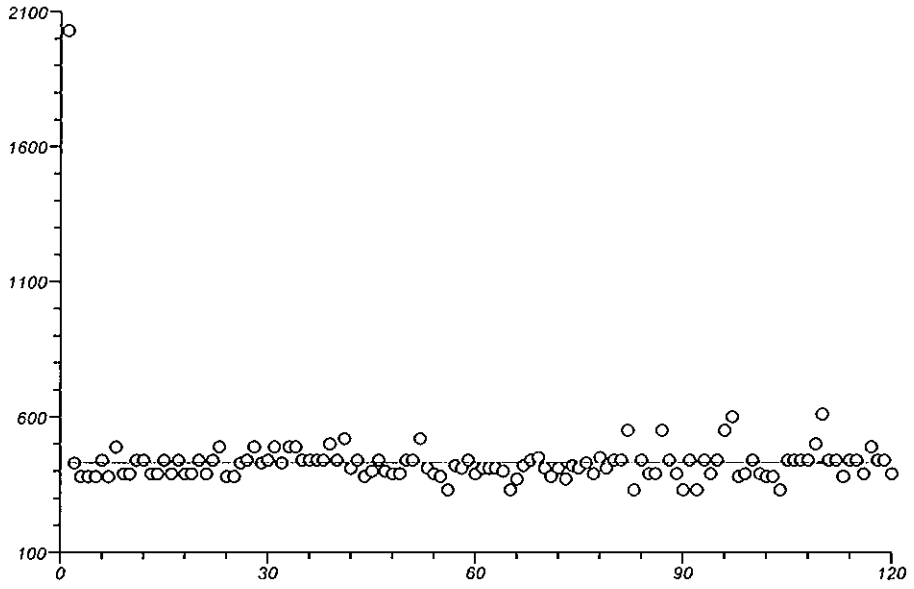


Figure 9.10: Non-parametric linear regression plot of PAVS performance following transfer to the flicker task (Presentation Number (x axis) vs. PAVS time (y axis)

Rapid learning is again observed in PAVS performance for displacement (Figure 9.11). As little as ten to fifteen presentations are sufficient to reduce mean response times to 370msecs, significantly below the fastest session mean obtained of 416.2msecs in session 3.

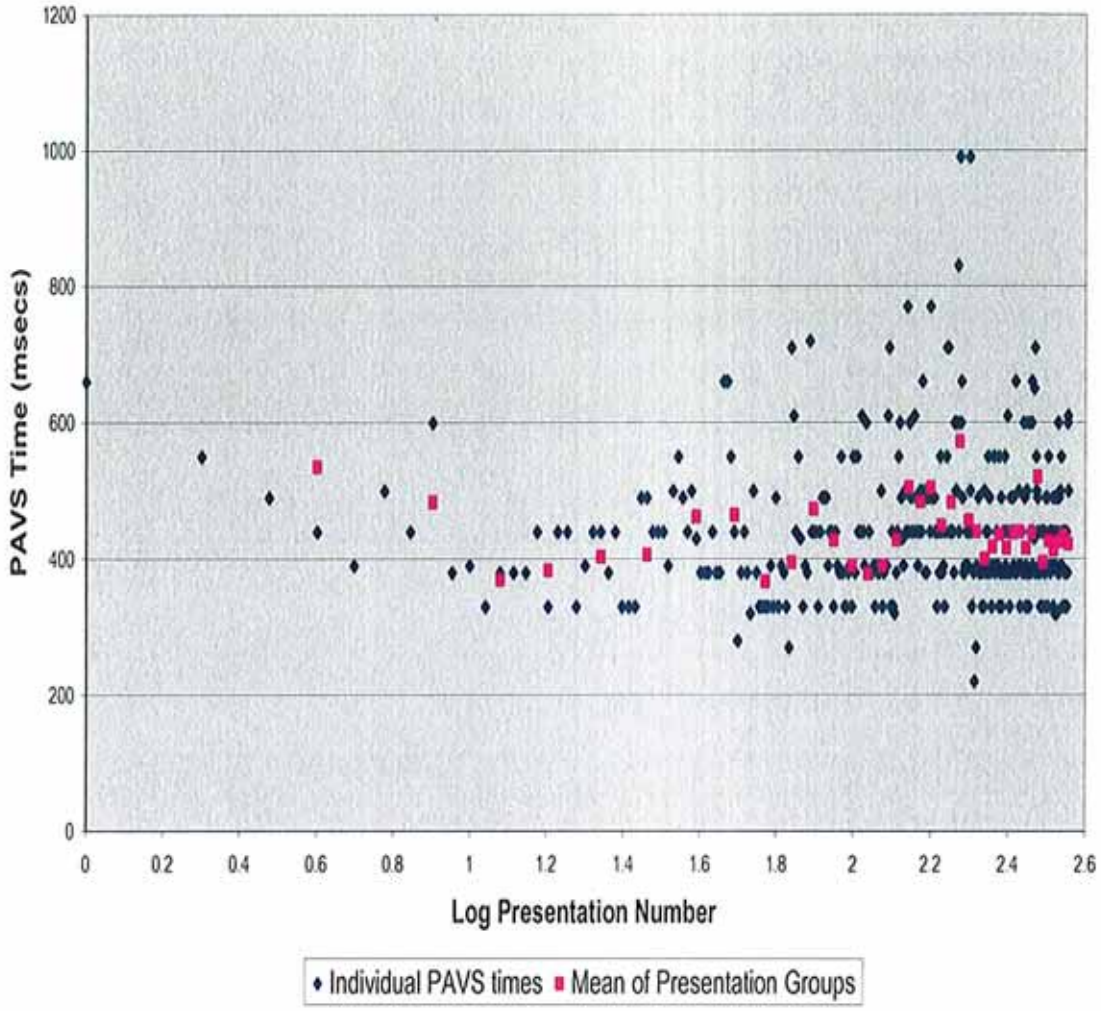


Figure 9.11: Learning curve during 360 presentations for the displacement target with superimposed mean response times of groups of presentations to reduce the visual impact of individual variability effects

Learning is again consolidated between sessions (Figure 9.12). Friedman's test for variance in performance indicates a significant difference between sessions (chi-square = 9.75, df = 3, F = 3.312, P = 0.02). The effect is isolated to a difference between the initial and second session (Conover paired comparison: p = 0.0025).

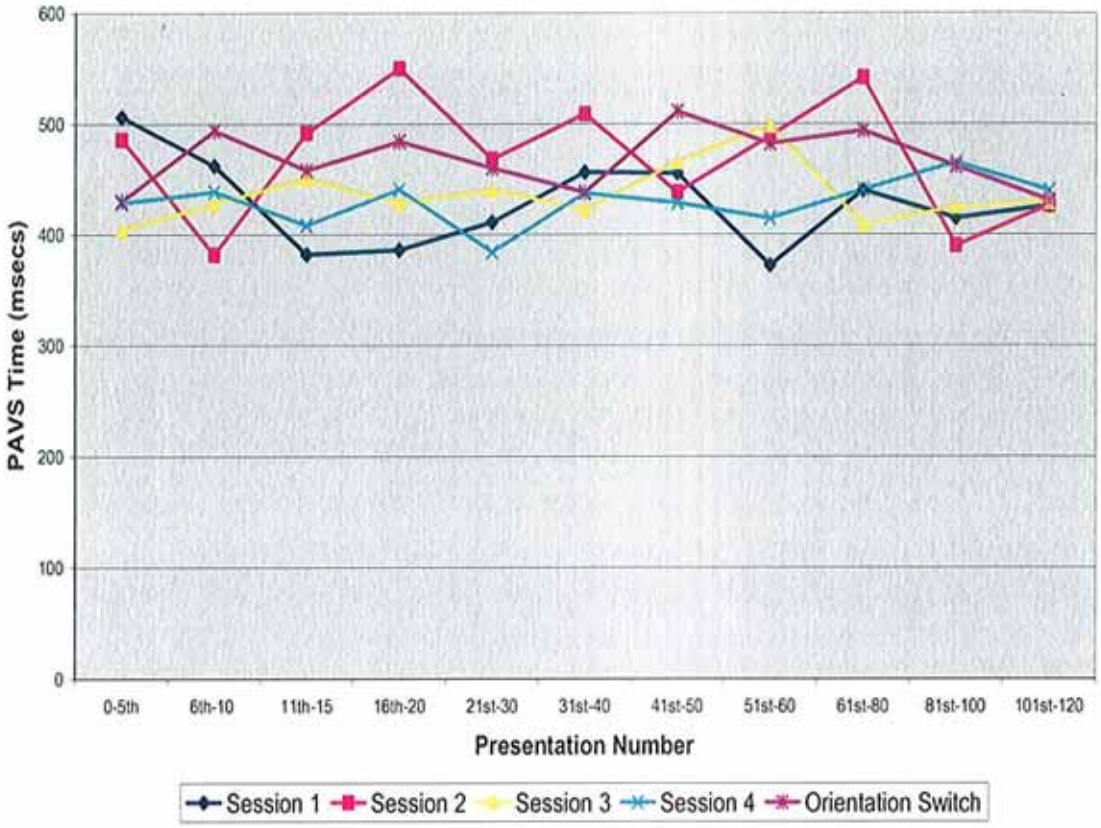


Figure 9.12: PAVS performance across sessions for displacement and after transfer to orientation

The zero slope in session 1 and increased intercept in session 2 (see Table 9c) however illustrate that the effect actually reflects a decreased performance level in session 2 which retains the highest intercept and slowest mean PAVS times.

Session	Slope	Y Intercept
1	~ 0.00	390msecs
2	-0.408	464.7msecs
3	~ 0.00	440msecs
4	~ 0.00	440msecs

Table 9c: Learning slopes and intercepts for each session of displacement

Once again, learning transfers into efficient performance from the outset for orientation (Figure 9.13). Non-parametric linear regression analysis produces a flat

slope (<0.144 – median = 0) and an intercept value of 440msecs (similar to that obtained in session 3 for the subject trained on orientation) indicating efficient performance from the outset.

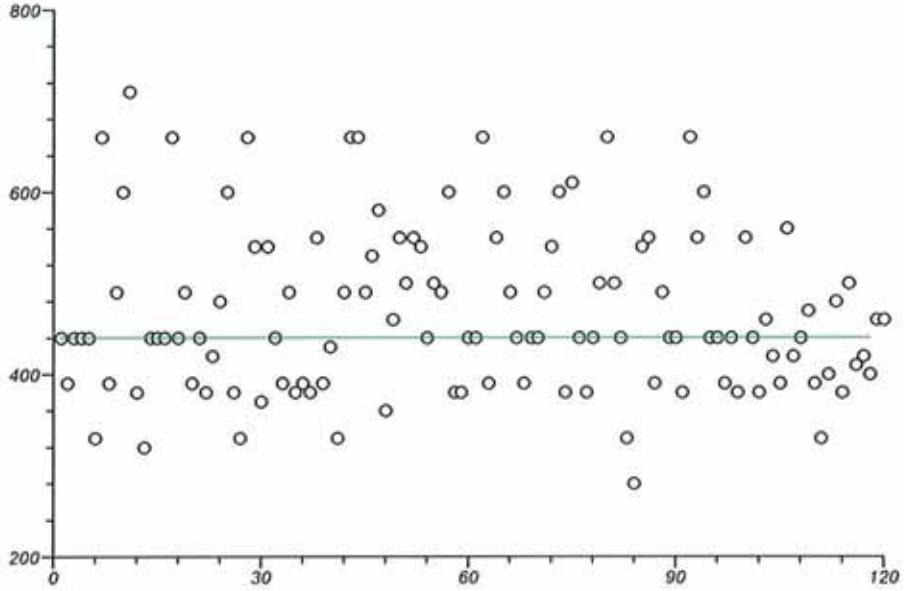


Figure 9.13: Non-parametric linear regression plot indicating PAVS performance following transfer to the orientation task (Presentation Number (x axis) vs. PAVS time in milliseconds (y axis))

Reflecting the possibility that learning may be a different or slower process in older subjects, the most difficult task, orientation, was repeated to determine the learning timeframe in an older observer (age 68 years). It appears that the older observer's learning timeframe is possibly faster and more consistent than the younger observer. Thirty-five to forty presentations saturates mean PAVS times at 564msecs (Figure 9.14).

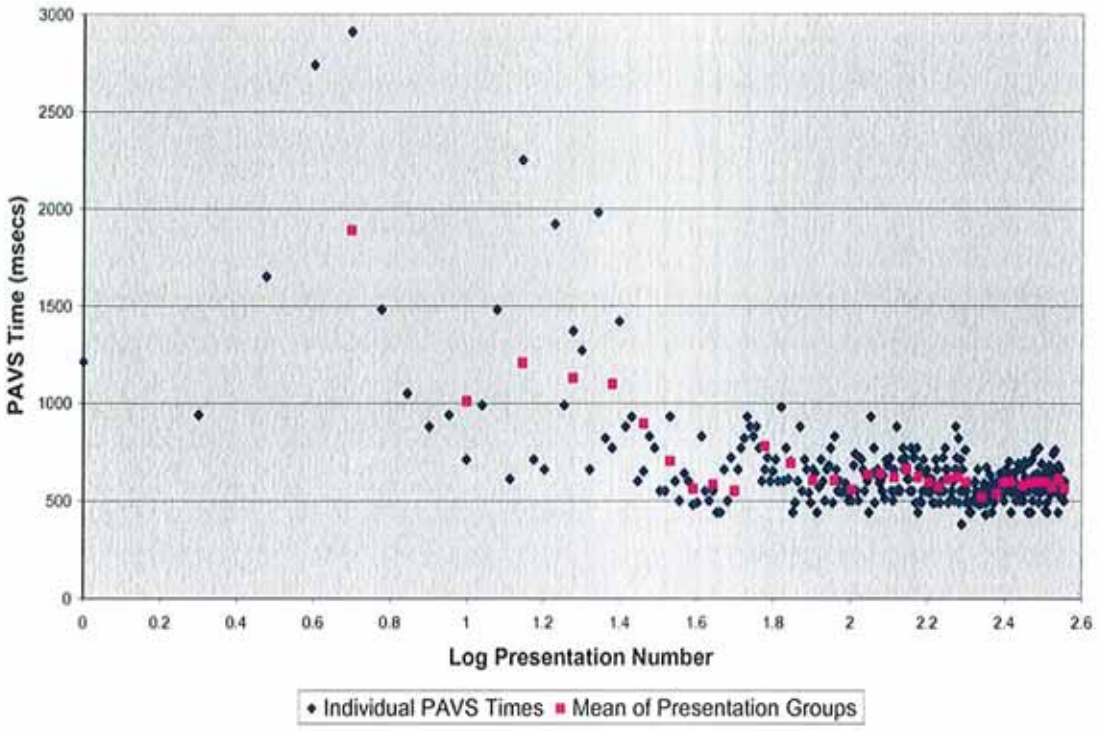


Figure 9.14: Learning curve during 360 presentations for the orientation target in an older observer and a superimposed curve of mean of groups of response times to reduce the visual impact of individual variability effects

Figure 9.15 illustrates early consolidation of the learning effect. Search times are consistently low after the learning plateau in session 1. Friedman's test for variance in performance indicates a significant difference between sessions (chi-square = 42.187, df = 4, F = 11.467, $P < 0.0001$). The effect is isolated to the initial session (Conover paired comparison: $p < 0.05$ for all pairs involving session 1). From session 2 on, there is no observed improvement in performance ($P > 0.05$ for all session pairs).

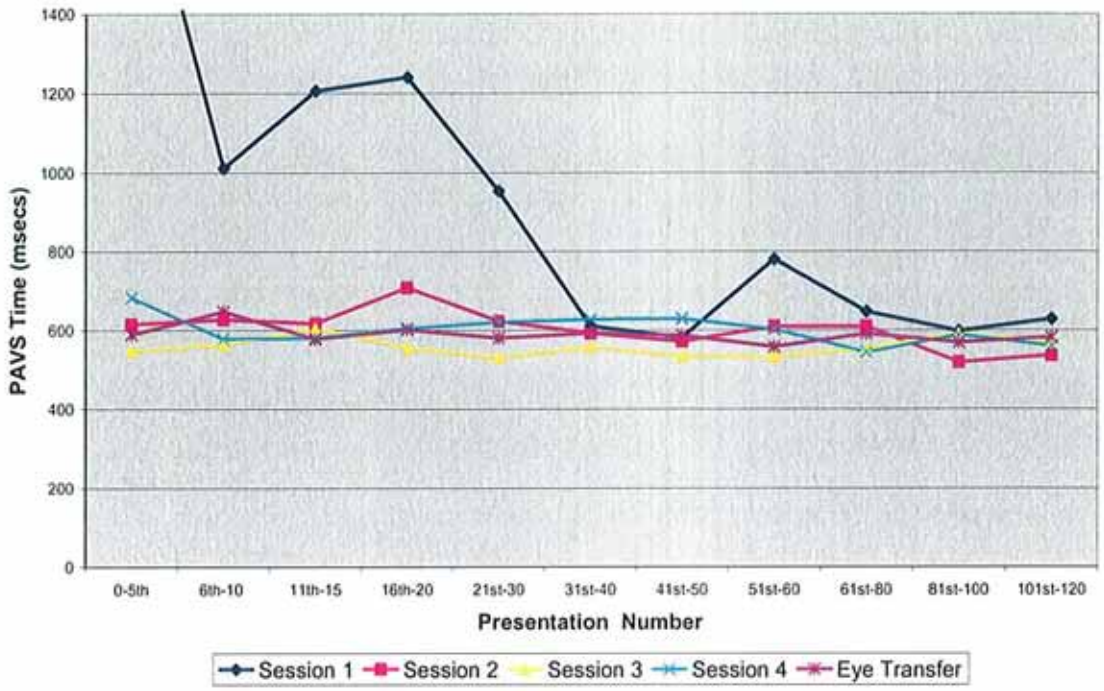


Figure 9.15: PAVS performance across sessions for orientation and after transfer to the fellow eye in an older observer

Session	Slope	Intercept
1	-2.986	840.71msecs
2	-0.833	600.42msecs
3	0	590msecs
4	-0.512	630msecs
Eye Switch	-0.132	598.01msecs

Table 9d: Learning slopes and intercepts for each session on the orientation task for an older observer

In this case, learning appears to transfer between eyes (Figure 9.16) as well as between tasks. The line slope (-0.132) and y-intercept value (598.01) mirror those obtained in the initial eye after significant learning had taken place in session 1.

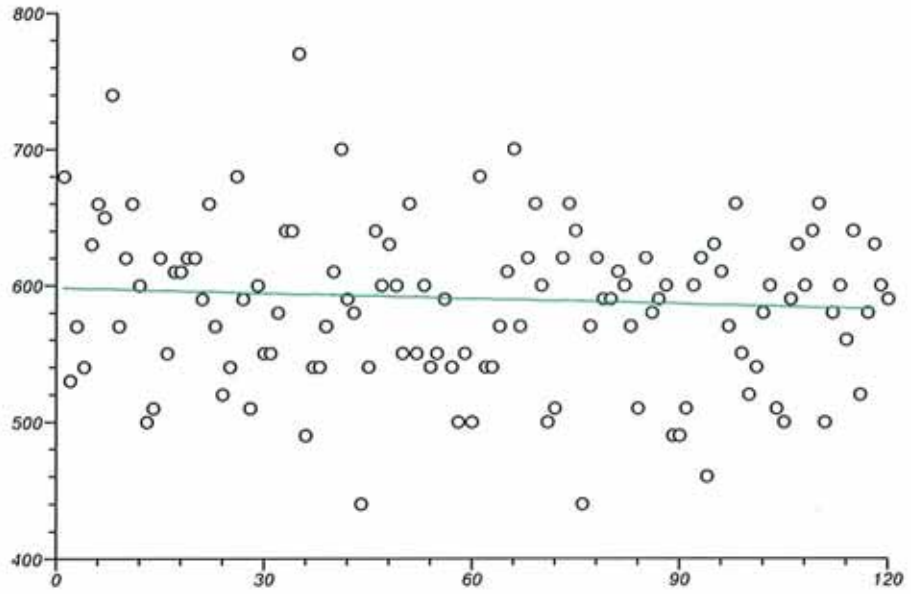


Figure 9.16: Non-parametric linear regression plot of PAVS performance on the orientation task following transfer to the fellow eye (Presentation Number (x axis) vs. PAVS time (y axis))

9.8 Discussion

The data described above have been collected in order to elucidate certain task-specific aspects of perceptual learning to determine their influence on (i) the clinical viability of the current PAVS test and (ii) to determine best practice to avoid learning artifacts in clinical data collection. The aspects explored include the rate or timeframe of perceptual learning, the specificity of learning induced to the task and to the eye trained, and also the persistence of any performance improvements obtained.

9.8.1 Perceptual Learning Timeframe

The perceptual learning effect results in improved performance with practice on all psychophysical testing procedures. While previous research has yielded conflicting information about the specificities of the learning effect, there is general consensus that the rate of learning is dependent upon the complexity of the task (Karni & Sagi,

1991; Madden & Allen, 1991; Sireteanu & Rettenbach, 1995; Ahissar & Hochstein, 1996 & 1997). PAVS tests as employed here can be regarded as relatively simple tasks and therefore the learning effect is likely to quickly reach a plateau.
Given unlimited viewing time (> 200 msec), subjects have been shown to typically perform very efficiently from the initial presentations (Ahissar & Hochstein, 1993). This would give weight to our assertion that minimal training is required for the current paradigm.

The results here appear to confirm a rapid saturation of the learning effect particularly in the case of the flicker and displacement tasks. Performance typically reaches a high level of efficiency after a very small number of trials, less than fifteen for displacement and marginally more for flicker.

At first glance the orientation data suggest a significantly lengthened learning timeframe for orientation (particularly in the younger observer). More careful examination shows that learning does improve significantly in the first 40 presentations (approximately 86% of the total improvement is reached by the 40^{th} presentation). However it may take some time for this effect to become consistent and this is reflected in the flat slopes from session 3 onwards in the younger subject. Such an effect was not observed in the older observer where less than forty presentations appear sufficient. This is in accordance with previous reports of significant variability in the rate of perceptual learning among observers (Fahle & Henke-Fahle, 1996). Despite this variability the data suggest that forty practice presentations would provide a sufficient platform to then begin clinical data collection free from any significant learning influence.

9.8.2 Learning Specificity

Previous research has provided conflicting results on the nature of the performance improvement in pop-out detection. In some cases, the results indicated low-level learning that did not transfer to other tasks or to the fellow eye (e.g. Ahissar & Hochstein, 1996). Others have shown the effects to be non-specific and freely transfer to other tasks and to the other eye (e.g. Sireteanu & Rettenbach, 1995). The results presented above indicate that for the tasks completed here the learning effects are rather non-specific. Following 360 presentations of a particular task, performance was immediately highly efficient when the subject transferred to any other target type, or to the fellow eye, indicating an improved search strategy on the subjects' behalf rather than a simple increase in sensitivity to the specific task. Typically, once a subject transfers to another target type, there are a couple of initially slow responses as the subject becomes acquainted with the new target type (note that the subject will not have seen any demonstration of the task prior to commencement). Performance returns immediately to asymptotic levels. It may therefore prove beneficial to ignore the first five to ten trials of the clinical test results in calculation of the mean response times.

9.8.3 Learning Persistence

The results here again confirm previous reports that the performance improvements gained are retained over a lengthy time period. Subjects here have been observed to maintain efficient performance from the outset up to six months after the initial training session. Six month intervals represent a typical recall period for subjects with suspect clinical findings so the endurance of the learning effect observed here is a positive finding with respect to clinical application of the test. Despite the persistence it may still prove beneficial to provide a short training session prior to each data collection as there is always the problem of individual variability.

9.9 Conclusions

Our findings are in general agreement with those of Sireteanu and Rettenbach (1995) in that the observed learning effect is fast, enduring and non-specific. Compared to other psychophysical tests of visual function such as perimetry, the learning effect should have minimal impact on result interpretation. Based on the results one could suggest a short practice period on each task prior to data collection, perhaps in the order of 20 presentations for each task (this should take approximately one minute to complete). Learning should transfer between the tasks so that by the end of the practice session the subject will have learned and adopted an efficient search strategy. As such, the test should provide a patient and practice friendly means of evaluating visual functional integrity.

CHAPTER 10

EFFECT OF TARGET ECCENTRICITY ON PAVS EFFICIENCY

10.1 SUMMARY

***Background/aim*:** Targets presented away from fixation have been shown to have lower discriminability due to the combined effects of sensory image degradation and attentional bias to central field locations. Such effects are known to impact upon visual search efficiency and as such may impact the interpretation of search results based on reaction time. The current study was designed to elucidate relative search performance at different retinal eccentricities.

Methods: Five subjects were examined using the same flicker, displacement and orientation search tasks as previously described. Target locations were in this instance pre-defined and therefore pseudo-random for each of the forty presentations. Search times were thus plotted as a function of retinal eccentricity and retinal quadrant.

***Results*:** Linear regression analysis reveals performance slopes consistently close to and non-significantly different from zero across all target types. Any effect of eccentricity was marginally larger for the orientation task than either flicker or displacement but in all cases any eccentricity effect was negligible.

Conclusions: The results reported here are in direct conflict with established reports of eccentricity effects on feature search performance. The absence of any effect here most likely reflects the nature of the suprathreshold stimuli used so that, even in the periphery, targets remain discriminable compared to distractors and performance continues close to performance limits across all eccentricities.

10.2 Introduction

The human visual system is continually pressed to deal with conflicting environmental demands, from foveal tasks such as reading to peripheral tasks such as negotiating a safe driving experience. To cope with the variable demands of high spatial and temporal resolution tasks, the visual system appears to have evolved a duplex design to efficiently meet the conflicting requirements. Spatial resolution is maximal at the fovea and decreases as a function of eccentricity (DeValois & DeValois, 1988). Contrast sensitivity is also observed to decrease with eccentricity and whereas low spatial frequency channels are distributed throughout the retina, high spatial frequency channels congregate in the fovea and decrease toward the periphery (Robson & Graham, 1981). The vast majority of the visual cortex is also devoted to analysis of foveal information (see section 3.4). The periphery however is more responsive to temporal visual properties (McKee & Nakayama, 1984). In tasks such as flicker fusion and motion detection, performance therefore improves as eccentricity increases. This duplex retinotopic organisation extends backwards through the magno and parvo divisions of the lateral geniculate nucleus and to the striate cortex via parallel pathways with distinctly different spatiotemporal characteristics (the ratio of P to M cells also decreases in the periphery- Azzopardi et al., 1999).

One of the major tools for investigating primitives of the visual system and the role of attention in visual object recognition has been the visual search task. A good deal of current research assumes that coverts shifts of attention (without eye movements) play an important role in visual search tasks. The presence or absence of such attentional shifts has been said to characterise the nature of the search process (e.g. Treisman & Gelade, 1980; Wolfe, 1994a). In laboratory search tasks, subjects typically look for a target item among distracting items. In most cases, the positions of targets and

distractors are random across trials. Information on the nature of search is generally derived from analysis of the effect of set size on response time. This makes the implicit assumption that, within reason, it does not matter where the distractors and targets fall in the visual field. It seems intuitively clear, and it has been experimentally demonstrated that this cannot be strictly true (e.g. Carrasco & Chang, 1995). Surprisingly, visual search theories appear largely not to have taken into account the effect of target location and inherent constraints on retinal function in interpretations of search efficiency.

Eccentricity effects on visual search may be accounted for in terms of the combined effects of sensory and attentional/decisional factors and must be addressed in order to draw any substantive conclusions from a visual search dataset.

10.2.1 Sensory Factors

The duplex retinal architecture results in distinct differences between the foveal and peripheral processing of visual stimuli. There are several interrelated differences between the fovea and the periphery that result in decreased spatial resolution with increasing retinal eccentricity (Kerr, 1971; DeValois & DeValois, 1988).
One determinant of spatial resolution capacity is photoreceptor packing density. There is a higher concentration of cones in the fovea (see Figure 10.1 & 10.2) than in the periphery with foveal estimates ranging from 147,000 cells per mm^2 (Osterberg, 1935) to 281,000 per mm^2 (Curcio et al., 1987). In the central fovea, the cones are so tightly packed that spatial resolution is limited by the aberrations in the optical components and diffraction effects at the pupil (normal resolution = 1 min arc, foveal cone spacing permits resolution down to 30 secs arc – Osterberg, 1935). As cone density falls spatial resolution becomes a sampling limited rather than optically limited system. Although

refractive errors are known to increase in the periphery (notably oblique astigmatism), once corrected, the spatial resolution capabilities of the eye remain dramatically reduced. The quality of the image produced by the peripheral retina is thus degraded.

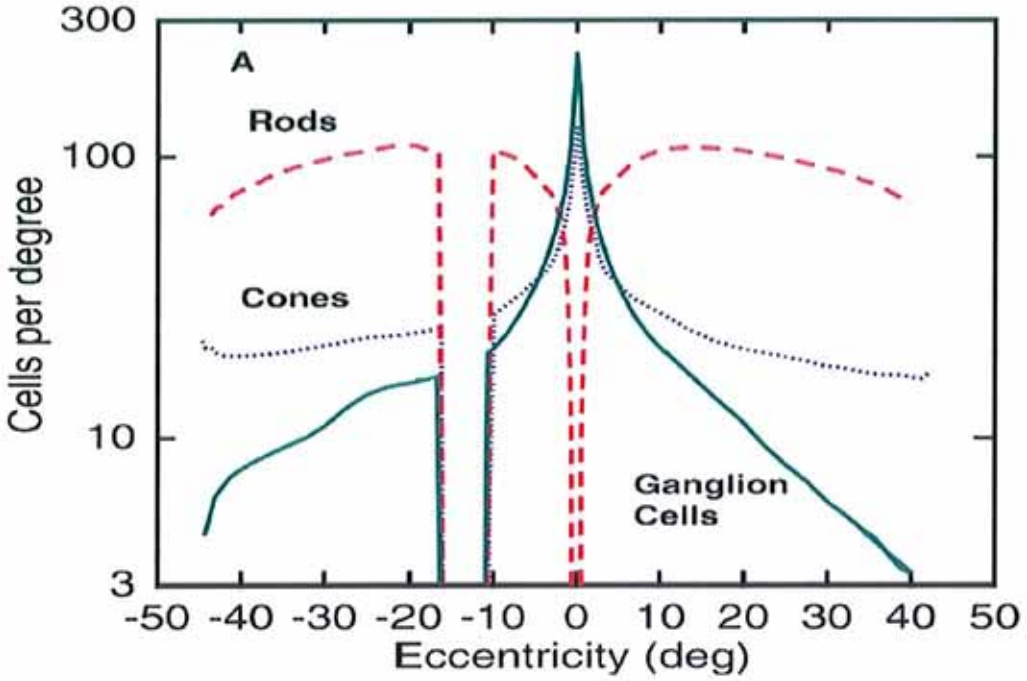


Figure 10.1: Densities of rods, cones and ganglion cells (x1000) in the human retina as a function of eccentricity along the horizontal meridian (modified from Curcio & Allen, 1990 & Curcio et al., 1990)

Another determinant of spatial resolution is post-photoreceptor processing of the retinal image. Raw anatomical cellular distributions comprise approximately 6.5 million cones, 110-125 million rods and about 1 million ganglion cells. The ratio of photoreceptors to ganglion cells dictates that there must be significant convergence of information from that initially captured to that delivered along the optic nerve. Again it is the retinal periphery that suffers most convergence. Peak ganglion cell density occurs at the fovea (Figure 10.1). At the foveal centre (out to ~2.2°) there are actually two ganglion cells (perhaps one ON ganglion and one OFF-ganglion) for each cone (Schein, 1988) so that all information gathered is translated back towards the visual

cortex. The gradient of functional ganglion density from fovea to periphery is in the order of 1000:1 with 50% of the total ganglion cells lying within 16° of the foveal centre, a region comprising only 7% of the entire retinal area (Curcio et al., 1990). Therefore, in the periphery, increasing eccentricity is accompanied, not only by retinal undersampling, but by increased convergence towards individual ganglion cells which serve ever increasing numbers of photoreceptors (see section 3.4.1 – Figure 3.14). An additional consequence of this increased convergence is the increased receptive field size of peripheral ganglion cells.

In visual search experiments, lateral masking may impair target detection more strongly as target eccentricity increases because of the increased receptive field sizes in the periphery (Breitmeyer, 1984), and as the retinal gradient is steeper when the target is surrounded by distractors rather than when alone, distractors may serve to heighten the eccentricity effect (Wolford & Shum, 1980). Other non-uniformities such as a slight favouring of the lower visual field (superior retina) which at eccentricities of 2.5° has 12% more cortical representation (Van Essen et al., 1984), and at eccentricities greater than 15° has 60% more retinal ganglion cells (Curcio & Allen, 1990), and a favouring of the temporal visual field (nasal retina) which has 300% more retinal ganglion cells beyond 15° compared to the temporal retina (Curcio & Allen, 1990) may also need to be addressed in the interpretation of search results.

The cortical magnification of the inferior field outlined above extends to a significant difference in the relative cortical representation of the central versus peripheral retinal architecture, and is seen to strongly favour foveal stimuli. Essentially the retinal projection to the visual cortex is large for the central visual field and is progressively compressed toward the periphery (Anstis, 1998). A cortical magnification factor,

which relates the number of degrees of visual angle per mm of cortex, describes the rate of sensitivity decrease with eccentricity. An additional magnification occurs when the parvocellular pathway of the LGN projects onto area 17. Estimates vary but the eventual cortical magnification of the central retina is such that about 25% of the striate cortex is devoted to the central 2.5° of the visual scene, about 80% is dedicated to the central 10° (DeValois & DeValois, 1988) and about 87% to the central 30° (Horton & Hoyt, 1991).

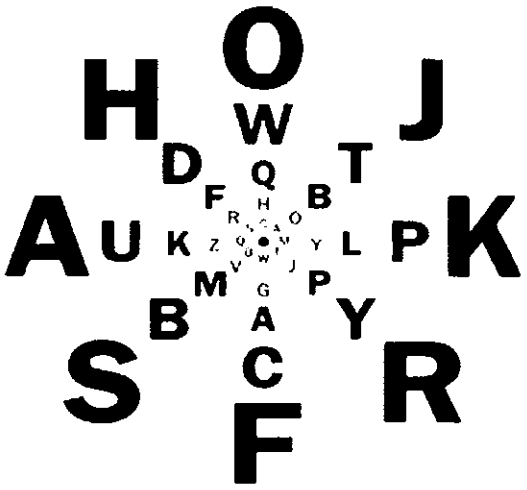


Figure 10.2: Special chart prepared to demonstrate how visual acuity decreases rapidly with target distance from the fovea. According to Anstis (1974), when the center of the chart is fixated at approximately normal reading distance, all the letters should be equally legible, since increasing target distance from the fovea is offset by a corresponding increase in letter size (from Anstis, 1974).

Thus, although spatial information is preserved from the retina to the cortex, the retinotopic projection prioritises foveal input, resulting in a disproportionately large representation of central retinal locations in visual cortex and an associated decrease in observers' performance for numerous visual tasks (Figure 10.2 illustrates a letter chart designed to illustrate the magnitude of the eccentricity effect).

In typical search tasks, increasing set size also increases the average retinal eccentricity of the target. Target eccentricity has a pronounced and persistent effect on search. Targets appearing at peripheral locations are detected more slowly and less accurately than those appearing near the central fixation point (Carrasco & Chang, 1995). Neither overt (with eye movements- when display duration was manipulated to eliminate eye movements, eccentricity effects persisted: Carrasco et al., 1995) nor covert attentional shifts alone can explain the eccentricity effect (a similar effect is observed in tasks requiring varying amounts of attentional involvement: e.g. feature vs. conjunction searches: Carrasco et al., 1995). Carrasco and her colleagues have proposed that these performance effects reflect the role of fundamental sensory factors (Carrasco et al., 1995; Carrasco & Frieder, 1997) and suggest that "the ubiquitous practice of averaging search time and error rate across all locations of the display has blurred any differential contribution of distinct retinal eccentricities to search performance".

Carrasco and Frieder (1997) eliminated eccentricity effects by magnifying the peripheral stimuli so as to compensate for retinal inhomogeneity. Under these circumstances, the set-size effect was eliminated for feature searches and substantially attenuated for conjunction searches. Furthermore, Carrasco and Yeshurun (1998) peripherally pre-cued target locations and found that both the set-size and eccentricity effects were attenuated but not eliminated for both feature and conjunction tasks. This was interpreted as further evidence that eccentricity effects reflect factors other than the serial deployment of attention. Larger set sizes reduce discriminability by lowering sensory quality thereby increasing noise in the decision process, thus impacting on search efficiency. Such effects are always likely to be more pronounced in conjunction tasks where "noise" levels are already heightened. Sensory factors however cannot account for all the eccentricity effects observed. Attentional bias to central locations

means that such targets will generally remain easier to locate across a broad range of stimulus conditions.

10.2.2 Attentional Factors

Guided Search was the first theory of visual search to attempt to incorporate the effect of eccentricity on search performance, with particular emphasis on search in a real-world situation (see section 2.13.2). Wolfe et al. (1998) added the assumption that activation in feature maps is modulated by eccentricity of target location. Given two identical targets at different distances from fixation, the item closer to fixation will receive more activation and will be attended before the more eccentric item. Search strategies serve to guide foveal attention to relevant field locations and, since central locations have a greater representation in the visual system than have peripheral locations, it is not unreasonable to imagine that central items produce a bigger attention guiding signal than do peripheral items.

Wolfe et al. (1998) produced search results using a number of paradigms that appear to rule out a strictly sensory account of eccentricity effects on search. Manipulation to eliminate any crowding effect (to account for increased lateral inhibition) produced only a small effect on search efficiency. Furthermore, M-scaling (by adjusting stimulus dimensions (e.g. size) appropriately, one can equate the amount of cortex activated, regardless of retinal eccentricity) did not eliminate the eccentricity effects. This finding is at odds with that reported by Carrasco and Frieder (1997). This difference in results however probably reflects the interaction of attentional and visual factors in the eccentricity effect in which the nature and discriminability of the relative targets used plays a role in the results obtained.

Wolfe et al. (1998) therefore argue that visual factors such as cortical magnification and crowding do not produce the eccentricity effect. An attentional bias toward central locations plays a significant role in the effects observed and visual factors play a role in modulating the deployment of attention.

Whatever the precise role, which most likely reflects some combination of sensory and attentional factors, eccentric target locations are less easily detected. The purpose of the present experiment was to determine whether previous findings of a significant eccentricity effect on preattentive search performance could influence data interpretation for the specific stimuli and tasks used in the current PAVS test, and if so how best to resolve the issue.

10.3 Method

(a) *Apparatus & Stimuli*

The apparatus and stimuli used were as described in chapter 6. The software program however was manipulated so that targets could be presented in pre-determined rather than random locations.

Using the same forty target locations permitted the selection of positions that would allow interpretation of the effect of eccentricity when comparing (i) central versus more peripheral efficiency and (ii) the relative performance of the four retinal quadrants. Targets were presented in a pseudo-random order in each session. Target positions were chosen so that ten targets were presented in each quadrant, and quadrant test locations mirrored those of vertically and horizontally adjacent quadrants (see Figure 10.3).

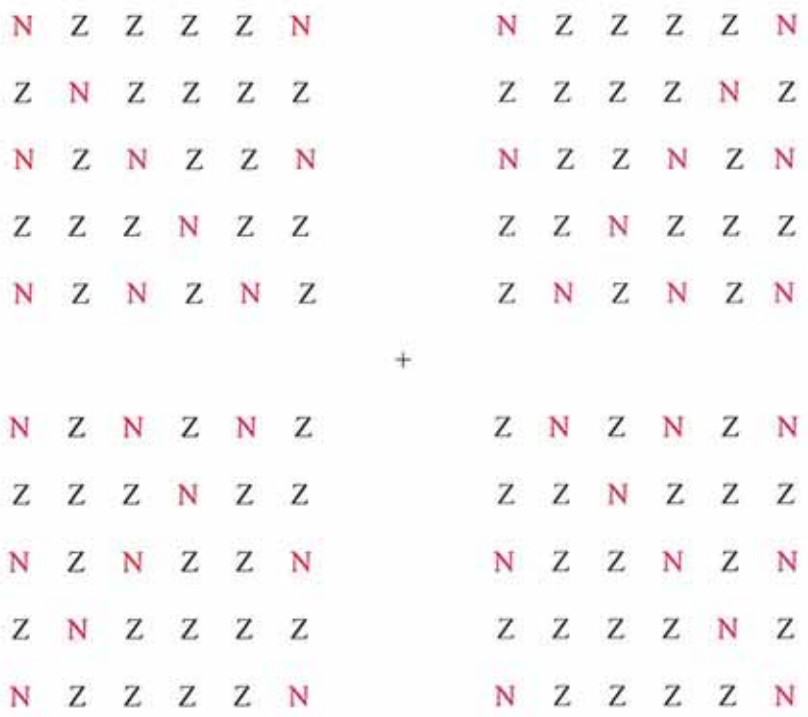


Figure 10.3: Possible target locations represented by the letter N and highlighted red. The same relative locations were used for each quadrant and eccentricity ranged from 5.82° to 19.80° from the central fixation cross. Quadrant and line spacing are exaggerated here for effect.

(b) *Subjects*

Five subjects were examined, four naïve and one trained observer (the author). All subjects had unaided acuity $\geq$ 6/6 and were free from ocular or systemic disease. The trained observer was aged 31 years and the naïve observers averaged 30 years. The trained observer was experienced in general psychophysical sensitivity measures and also in the PAVS task employed here. The naïve observers had never previously completed a psychophysical test of visual sensitivity (other than a visual acuity test).

(c) *Procedure*

Observers were permitted 120 practice presentations, 40 for each target type. Following the practice session, each observer completed three sessions of 120

presentations, forty for flicker, displacement and orientation respectively. The left eye was occluded throughout the experiment. The effect of eccentricity was examined for the trained and naïve observers separately, using the mean response time (group mean in the naïve group) from the three sessions for each of the forty target locations for each task. Subjects were advised to attempt to respond without the use of eye movements where possible i.e. to fixate the central cross continuously.

10.4 Results

(A) Trained Observer

Figure 10.4 shows the overall effect of eccentricity on PAVS performance for the flicker task along with the effect isolated to each visual field quadrant. A simple glance illustrates a virtually complete absence of any effect of eccentricity of search efficiency. The linear regression trendline shows a close-to-zero slope. The line can be described by the equation $B = -0.123A + 333.90$ and Pearson's correlation coefficient is not significantly different from zero ($r = -0.039$, $p = 0.9145$) indicating the absence of a relationship between eccentricity and search efficiency.

Performance between sessions for the same flicker target locations was analysed using the Friedman Test and revealed no statistical difference between sessions ($p = 0.079$, $F=2.622$, $dF=2$)

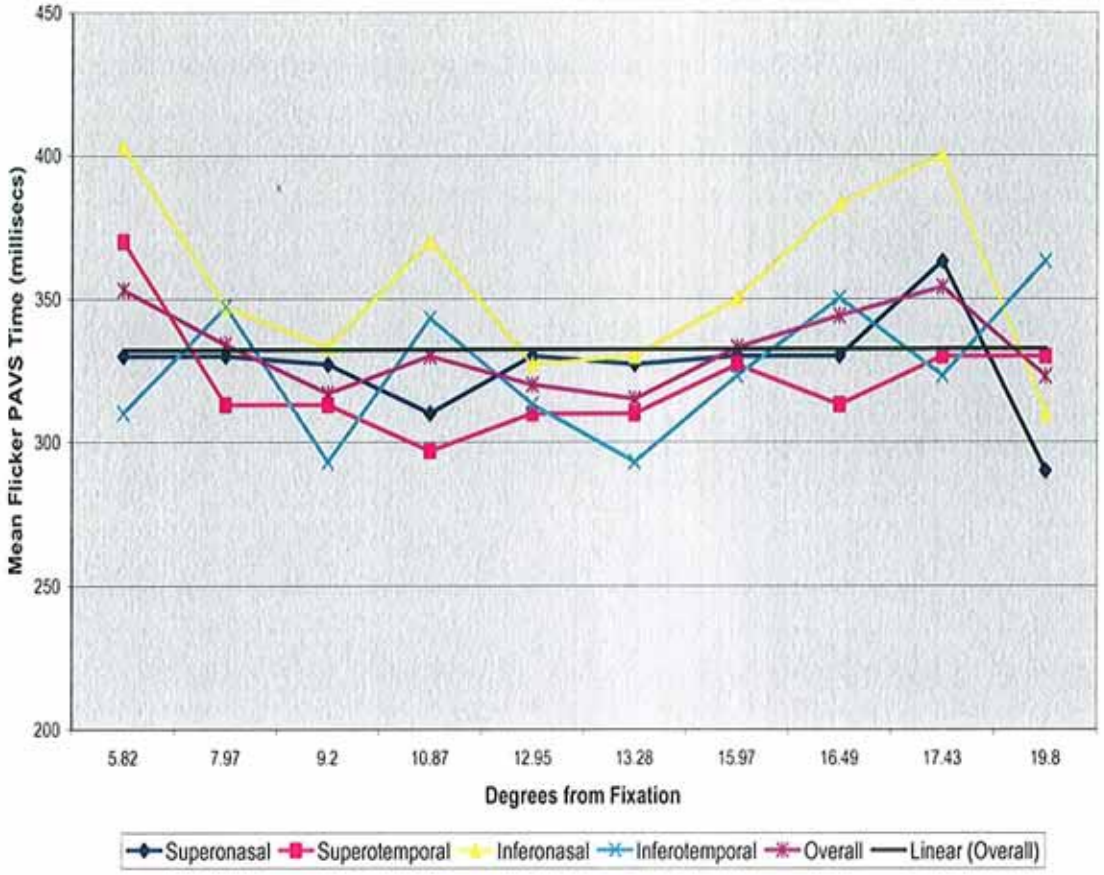


Figure 10.4: Effect of eccentricity on PAVS efficiency for the flicker task across increasing eccentricities in a trained observer

Figure 10.5 illustrates PAVS performance at increasing eccentricities for the displacement task. The trendline again highlights the absence of a linear relationship between performance and eccentricity.

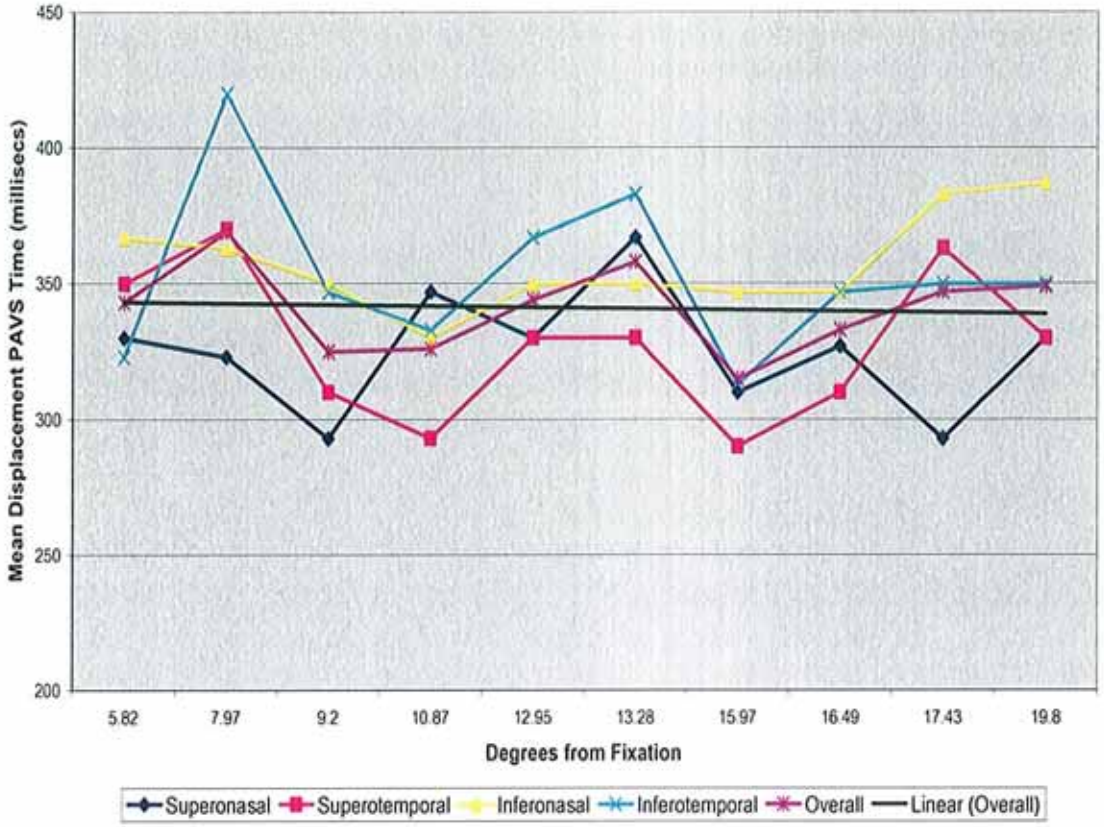


Figure 10.5: Effect of eccentricity on PAVS efficiency for the displacement task across increasing eccentricities in a trained observer

The equation of the line is given by C = -0.449A + 346.72 and the correlation coefficient is again not significantly different from zero (r = -0.124, p = 0.7335). The Friedman Test again finds no statistical difference in performance between sessions (P=0.192, F= 1.685, dF =2).

Figure 10.6 demonstrates a slight increase in mean response times at increasing eccentricity for orientation. The line is described by the equation D = 2.329A + 332.47. Pearson's correlation coefficient is statistically significantly different from zero (r = 0.699, p = 0.024). The effect however is obviously minimal and for all intents and purposes, PAVS performance can be deemed independent of eccentricity for each task

in a trained observer. Between session performance is again consistent (P=0.103, F= 2.345, dF=2)

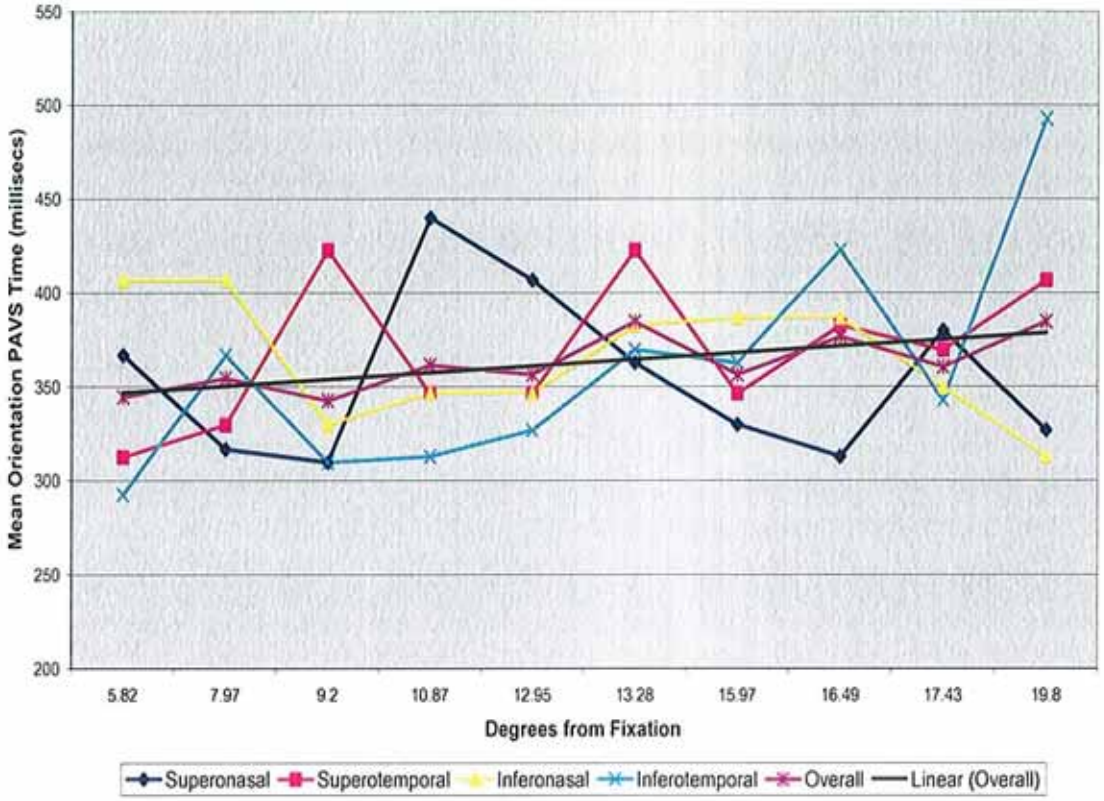


Figure 10.6: Effect of eccentricity on PAVS efficiency for the orientation task across increasing eccentricities in a trained observer

Table 10a outlines the regression analysis of the eccentricity effect isolated to separate field quadrants. A linear relationship between eccentricity and PAVS performance is observed only on the orientation task and there only in the inferotemporal quadrant. Analysis of the raw data however suggests that this may not be a true eccentricity effect. The mean of the three sessions for the 19.80° eccentricity target location is 493millisecs. This is composed of individual response times of 770msecs, 330msecs and 330msecs in sessions 1, 2 and 3 respectively. The session 1 time is therefore having a dramatic influence on the slope of the inferotemporal trendline. If the mean of

sessions 2 and 3 (330msecs) is computed instead, the statistical significance disappears (although the positive trend persists) – r = 0.445, p = 0.111.

Task	Quadrant (Field)	Slope	Intercept	Correlation Coefficient (r)	P value
Flicker	Superonasal	-0.40	331.91	-0.10	0.82
	Superotemporal	-0.77	331.35	-0.17	0.66
	Inferonasal	-1.54	375.33	-0.22	0.50
	Inferotemporal	2.20	297.19	0.41	0.13
Displacement	Superonasal	-0.46	331.03	-0.09	0.84
	Superotemporal	-1.27	344.14	-0.21	0.50
	Inferonasal	1.29	340.70	0.33	0.33
	Inferotemporal	-1.21	369.05	-0.18	0.65
Orientation	Superonasal	-1.13	370.01	-0.12	0.75
	Superotemporal	3.84	319.12	0.45	0.11
	Inferonasal	-3.36	409.35	-0.46	0.09
	Inferotemporal	9.84	232.51	0.74*	0.02

* statistically significantly different from zero (P = 0.015)

Table 10a: Linear regression analysis of relationship between eccentricity and PAVS performance across visual field quadrants for the trained observer

(B) Naïve Observers

Figure 10.7 shows a similar effect for flicker in naïve observers with a shallow slope across eccentricity. The regression line is described by the equation E=1.015A + 372.73. Pearson's correlation coefficient is not statistically different from zero (r = 0.224, p = 0.533).

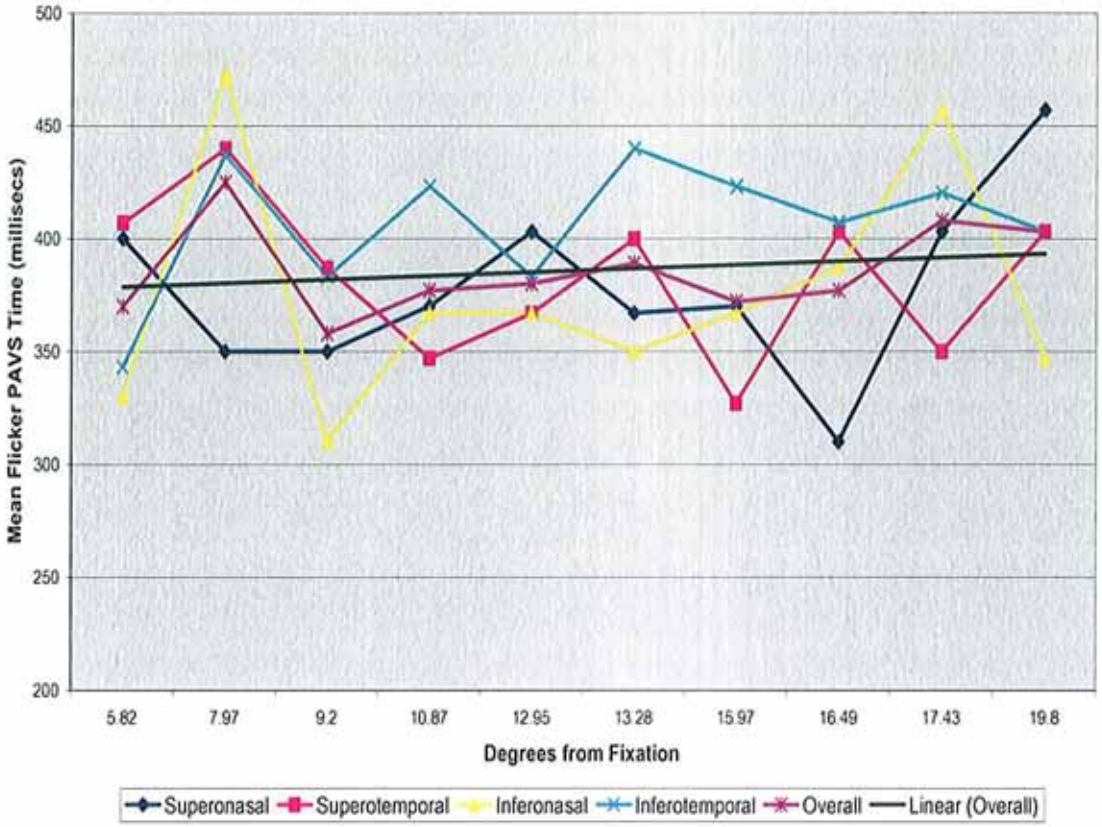


Figure 10.7: Effect of eccentricity on PAVS efficiency for the flicker task across increasing eccentricities in the naïve observer group

Performance in each session was again consistent with Friedman's Test again confirming the absence of any significant variance (P= 0.073, F=2.711, dF=2) between sessions.

Figure 10.8 continues the trend, highlighting consistent performance across increasing eccentricity for displacement. The line is described by the equation F= 2.579A + 369.52 and Pearson's correlation coefficient is not significantly different from zero (r = 0.327, p = 0.357). Friedman's Test found no statistical difference in performance between sessions (P = 0.192, F = 1.685, dF = 2).

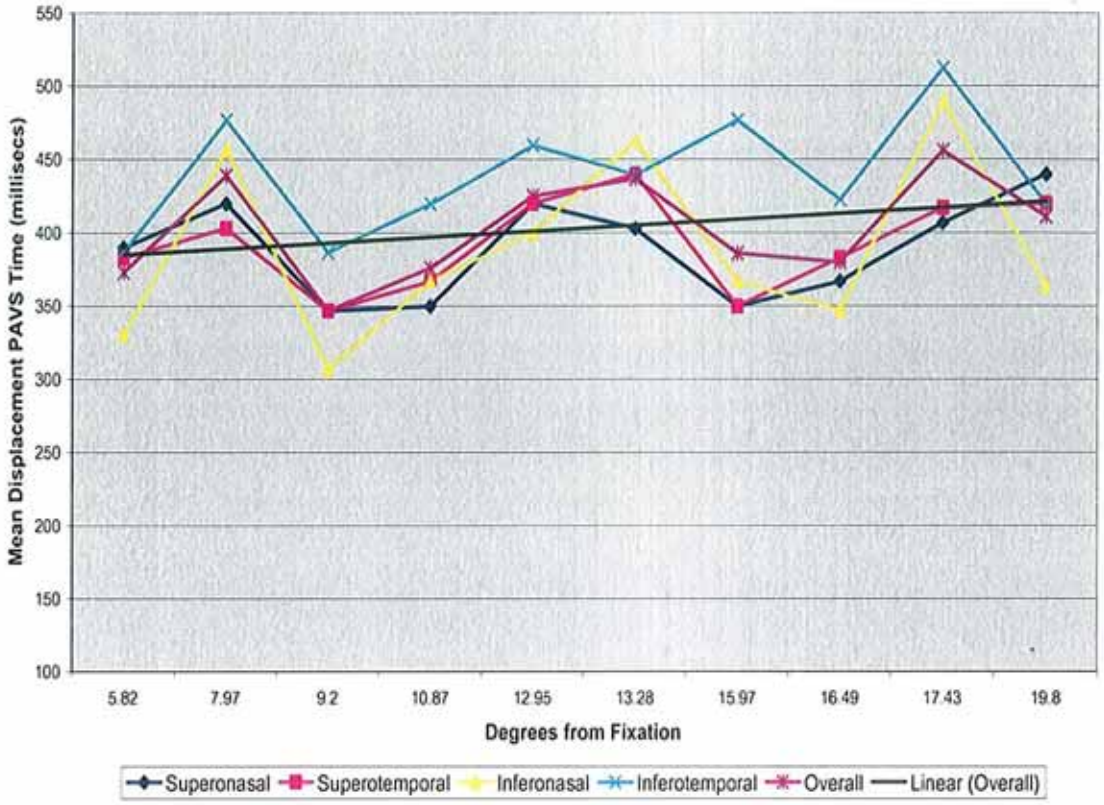


Figure 10.8: Effect of eccentricity on PAVS efficiency for the displacement task across increasing eccentricities in naïve observers

Figure 10.9 illustrates that the effect of eccentricity on orientation performance is, as in the trained observer, larger than for either displacement or flicker. The correlation coefficient ($r = 0.679$, $p = 0.031$) is statistically different from zero. In this instance the effect is again isolated to the inferior field, with the mean response time of 607msecs for the 15.97° eccentricity point in the inferotemporal field and the mean of 673msecs for the 19.8° location in the inferonasal field significantly elevated compared to all other values (see Table 10b). In particular, the inferotemporal 15.97° location is abnormally affected by the mean response time of 1140msecs from one individual (group mean of other 3 subjects = 517msecs). If the mean of these three subjects is used instead, the correlation coefficient ($r = 0.614$, $p = 0.078$) becomes statistically non-significant. The statistical effects observed therefore seem to reflect the absence of a definite effect of eccentricity on performance.

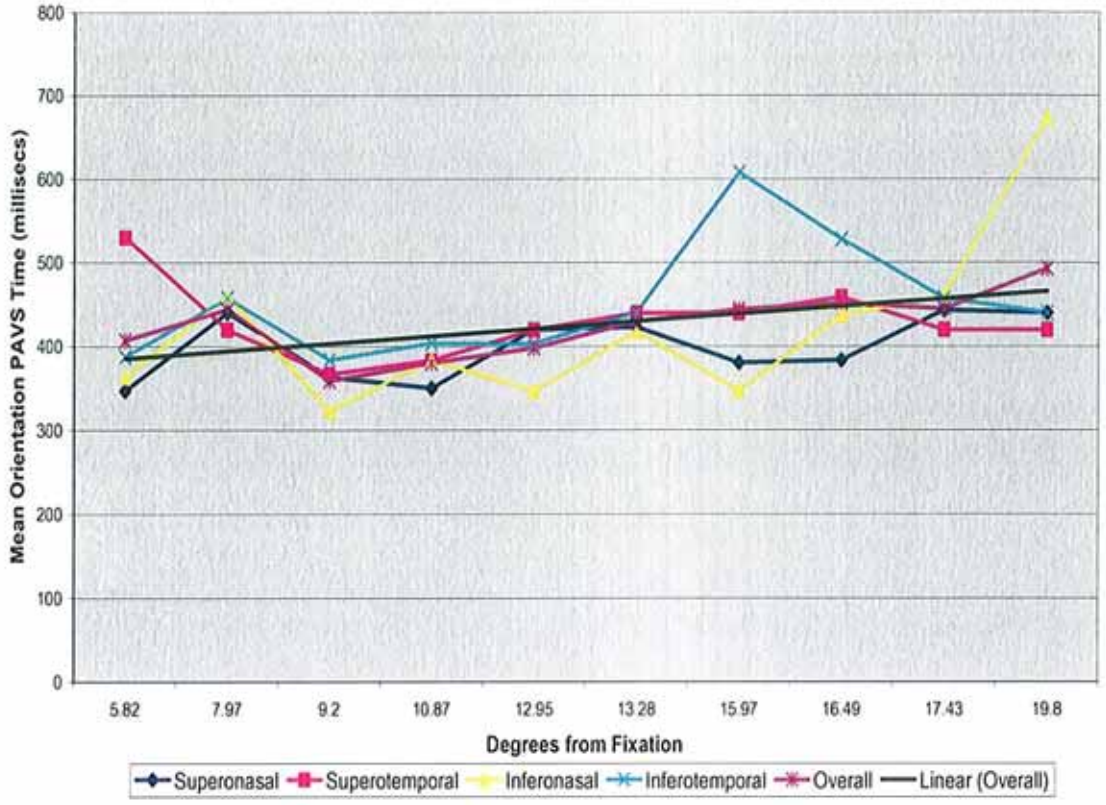


Figure 10.9: Effect of eccentricity on PAVS efficiency for the orientation task across increasing eccentricities in naïve observers

Friedman's test again finds no statistical variance between sessions (P = 0.628, F = 0.467, dF = 2).

When the effect of eccentricity is analysed specific to each quadrant, regression analysis (Table 10b) again reveals the absence of a linear relationship between eccentricity and search performance even in naïve observers previously unexposed to this type of sensitivity measure.

Task	Quadrant (Field)	Slope	Intercept	Correlation Coefficient (r)	P Value
Flicker	Superonasal	2.68	343.29	0.30	0.40
	Superotemporal	-2.73	418.51	0.36	0.30
	Inferonasal	1.53	355.71	0.13	0.72
	Inferotemporal	2.48	373.97	0.38	0.26
Displacement	Superonasal	1.73	366.97	0.23	0.52
	Superotemporal	2.38	363.09	0.33	0.36
	Inferonasal	2.84	352.25	0.21	0.58
	Inferotemporal	3.70	392.43	0.41	0.21
Orientation	Superonasal	4.24	343.84	0.50	0.16
	Superotemporal	-1.68	451.65	-0.17	0.66
	Inferonasal	13.12	250.68	0.58	0.10
	Inferotemporal	8.04	346.06	0.52	0.12

Table 10b: Linear regression analysis of relationship between eccentricity and PAVS performance across visual field quadrants for naïve observers

10.5 Discussion

Given (i) the nature of the search task employed here, presenting 120 potential targets on screen simultaneously across a maximum angular eccentricity of 19.80° from fixation, and (ii) the finding in previous experiments that eccentricity modulates performance in visual search (e.g. Carrasco & Frieder, 1997; Wolfe et al., 1998), it could well be expected that the current search task would suffer from similar eccentricity effects on PAVS efficiency. Previous studies have tended to examine less expansive eccentricities than assessed here (up to 9° in Carrasco & Frieder, 1997 and 9.7° in Wolfe et al., 1998), thus increasing the expectation of a detrimental eccentricity effect on performance over a wider retinal area here.

The results presented here however are in direct conflict with previous observations. Typically, peripheral response times have been observed to slow by 30–40 msecs per

degree increase in eccentricity for feature search tasks (e.g. Wolfe et al., 1998). This should translate into a 420–552msec increase in response time when comparing the least to the most eccentric targets presented here. It is immediately obvious that no such effect occurred here. In fact, in the experienced observer, the slopes for flicker and displacement indicate an inverse relationship between eccentricity and performance with performance possibly improving somewhat at increased eccentricity.

The statistical effect observed in the orientation task for both the trained and naïve observers is marginal especially when compared to the expected eccentricity effects above. The observed change in mean response time from least to most eccentric locations is in the order of 42 msecs and 86 msecs for the trained and naïve observers respectively (approximating the change previously observed for a mere 1 and 2 degrees increased eccentricity respectively).

There are several possible explanations for the results obtained here. One could speculate that it may be accounted for in terms of the observed heightened responsiveness of the retinal periphery to temporal properties (other eccentricity studies have not used search tasks involving flicker or motion displacement) and may be due in part to the substantial difference in processing speed in the periphery (~80msecs faster processing speed in the periphery compared to centrally for feature search – Carrasco et al., 2006). This increased peripheral processing speed (due in part to the faster conduction and integration times for magno cells compared to parvo – Carrasco et al., 2006) could in theory negate somewhat the effects of decreased target discriminability and central attentional bias. The mean response times observed here would tend to support the notion of increased sensitivity to temporal stimuli in the periphery given that both flicker and displacement means are consistently faster than

those observed for the orientation task (trained observer –335 msecs, 344 msecs, and 359 msecs; naïve observers - 386 msecs, 402 msecs and 425 msecs for flicker, displacement and orientation respectively: orientation has been consistently slowest in all experimental paradigms reported here). The minimal effect in the orientation task combined with the results from other studies however would tend to rule out differential processing speeds as an explanation for the absence of an eccentricity effect. The nature of the flicker and displacement tasks is likely to minimise the eccentricity effect.

A second and more likely explanation takes into account differences in the experimental strategies employed. Typical psychological search paradigms use speed and accuracy measures with limited presentation times to prevent saccadic fixations in an attempt to elucidate the search process. In this instance, presentation time was unlimited, the target remaining present until the subject responded. As such it could be argued that the current test represents an easier task. Eye movements could potentially be used to compensate for peripherally reduced discriminability. To argue for such an effect however would fail to account for the time required to make such compensatory eye movements. Typical saccades take approximately 50 msecs to execute (Wolfe & Gancarz, 1996) and therefore cause a subsequent increase in response time if used to facilitate search. Search times elicited here were typically fast and as they were consistent across eccentricities, it can be concluded that additional eye movements were not employed at increasing eccentricity.

Perhaps the most potent explanation of the absence of an eccentricity effect here may lie in the nature of the stimuli used. The use of high luminance and high contrast suprathreshold stimuli essentially ensures that targets remain easily discriminable even

in the most eccentric locations tested here. The flicker target for example extends to an area of 64mm^2 (subtending 56 mins arc); a size comparable to the largest Goldmann stimulus size V targets reserved for use in short wavelength perimetry where sensitivity to the target is known to be low. In terms of standard measures of visual field sensitivity, the effects of spatial summation would render the retina ten decibels more sensitive to this flicker stimulus compared to an equiluminant standard Goldmann III stimulus typically employed across more eccentric retinal locations during routine perimetric examination. Sensitivity to such a high luminance, high contrast, and large target is therefore likely to be very high and obviously remains sufficiently high so that target differences remain sufficiently discriminable and pop-out facilitates continued efficient parallel search even in the periphery. Even the higher spatial frequency displacement and orientation targets are sufficiently large and bright to remain equally discriminable irrespective of location. Spacing between target and distractors may also be an important factor in maintaining discriminability and inter-element spacing here remains sufficiently high at double the angular subtense of the individual elements (1.83°) so that lateral target inhibition appears not to influence performance.

Previous experiments have demonstrated variability in search performance across the visual field with response times typically shorter in the superior field compared to the inferior field and also in the temporal compared to the nasal field (e.g. Wolfe et al., 1998). When the data were pooled here, subjects demonstrated altitudinal and lateral field asymmetries. Search efficiency for targets in the superior field was more efficient than for those in the inferior field across all target types across all subjects consistent with previous findings. Lateral asymmetries proved somewhat less consistent. In the naïve observers search in the nasal field was more efficient for each task while in the

trained observer a difference in performance was only observed in the flicker task where search in the temporal field was more efficient. The effect in all cases however was small and did not quite reach statistical significance. Given the increased sensitivity of the inferior and temporal visual field these search results are perhaps somewhat surprising and not easily explained.

Eccentricity therefore appears to exert a somewhat reduced influence on search performance for the stimuli and procedures adopted here. In a display strategy using random locations, average eccentricity values need not be computed and search efficiency can be presumed to be independent of retinal eccentricity.

CHAPTER 11

INVESTIGATION OF PREATTENTIVE VISUAL SEARCH (PAVS) PERFORMANCE IN PATIENTS WITH ESTABLISHED GLAUCOMA, GLAUCOMA SUSPECTS AND NORMALS

11.1 SUMMARY

***Background/aim*:** Damage to the nerve fibre layer or visual pathway might be expected to reduce the efficiency with which the visual system performs analysis of the ever-changing field of vision. The purpose of the research reported here was: (i) to test the unsubstantiated findings of Flitcroft et al. (1996) that patients with glaucoma demonstrate impaired parallel search function, and (ii) to provide a cut-off performance level that would serve to distinguish glaucoma in early cases.

Methods: Three groups of observers (Glaucoma, Suspects and Normals) were examined, using computer generated flicker, orientation, and vertical displacement targets to assess PAVS efficiency. The task required rapid and accurate localisation of a singularity embedded in a field of 119 homogenous distractors on either left or right hand side of a computer monitor. All subjects also completed simple (SRT) and choice (CRT) reaction time tasks.

Results: Independent samples T tests revealed PAVS efficiency to be significantly impaired in the glaucoma group compared to both normals and suspects. Performance was impaired in all types of glaucoma tested. Analysis of the normal and suspect group revealed a significant difference only for motion displacement response times. Similar analysis of the perceptual search ability (PSA) index confirmed the glaucoma findings but also showed statistically significant differences between suspects and normals across all target types. ROC curve analysis provides an optimal performance cut-off value for each task and an indication of test sensitivity and specificity.

***Conclusions*:** A test of PAVS efficiency appears capable of differentiating early glaucoma from both normals and suspects. Analysis incorporating the PSA index

confirms the high diagnostic capacity of the test and suggests that it may be more sensitive to early glaucomatous losses than conventional achromatic perimetry.

11.2 Introduction

Glaucoma remains an enigmatic condition, frustratingly elusive in the earliest stages, often progressing despite apparently "successful" therapeutic intervention once diagnosed. Traditional diagnostic techniques such as visual field assessment, optic nerve and retinal nerve fibre layer evaluation are limited to the extent that the earliest losses of glaucoma remain difficult to detect (Quigley et al., 1982; Foster et al., 2002) – see Chapter 5. Attempts to design novel psychophysical tests for early glaucoma detection have thus far proved unable to provide a functional test capable of replacing conventional achromatic perimetry which often fails to detect early functional losses in glaucoma (see Discussion in section 11.5).

Pre-attentive vision is a global visual function that can perform a simple analysis of image content simultaneously across an entire image. Consequently it is a reasonable assumption that PAVS is dependent on neural mechanisms being intact across the retina. If this is the case, a suitably configured PAVS test might be able to detect any retinal disease or other condition that produces damage across a significant area of the visual field or to the neural systems subserving vision. If pop-out does not occur, for example because glaucoma is present, search will be more serial in nature and response times will increase accordingly.

The current PAVS test allows rapid and easy stimulus configuration during the course of a single examination, enabling preferential stimulation of cells with different optimal sensitivities (the current test presents a flicker and displacement target modulated at 16Hz to preferentially stimulate the magno-pathway, and a high spatial

frequency orientation target to preferentially stimulate the parvo-pathway). Given the apparently non-selective nature (Johnson, 1994) of retinal ganglion cell death in glaucoma (numerous investigations have demonstrated losses of both magnocellular - Quigley, 1987; Anderson & O'Brien, 1997 and parvocellular function - Drum et al 1989a; Johnson et al., 1993a), it would seem desirable to evaluate the functional integrity of different cell types during the course of a single examination to optimise sensitivity to the earliest losses in glaucoma.

A test of PAVS efficiency is inherently different from conventional psychophysical techniques. The latter techniques characteristically rely on the presentation of single targets in isolated areas of the visual field. The current test presents 120 stimuli and relies on the detection of a feature difference. As such it requires retinal and neural integration of the combined responses of neighbouring and overlapping receptive fields of retinal ganglion cells. Such a strategy potentially overcomes the ganglion cell receptive field overlap problem and studies have confirmed that other population-response tests such as motion coherence (Silverman et al., 1990) and pattern-discrimination perimetry (Drum et al., 1989a; 1989b; Nutaitis et al., 1992; Chauhan et al., 1993) are possibly more sensitive than standard achromatic perimetry.

The use of a response time here, rather than a threshold experimental paradigm, also simplifies the nature of the PAVS test from the subject's perspective. This has potential advantages if the test is to be applied to patients with limited span of attention, including elderly patients amongst whom most types of glaucoma are most prevalent (Tielsch et al., 1991; Klein et al., 1992). In the present study it was found that it is also a very rapid test taking as little as one minute per eye to perform a complete assessment using all three targets on a normal subject, to a *maximum* of six minutes per eye to similarly assess the most advanced cases of glaucoma, while a

typical early glaucoma subject examination takes in the order of only two minutes forty seconds per eye. The current test remains resistant to the potentially confounding effects of optical blur, with the obvious exception of the high spatial frequency orientation target that is resistant only to approximately 1D of optical defocus (Chapter 7 and Davison & Loughman, 2006). The perceptual learning curve saturates quite rapidly (Chapter 9) which probably relates to the task simplicity (Ahissar & Hochstein, 1996). Such rapid means of assessment, simplicity of task and resistance to optical blur have obvious merit for development of a clinically viable test for glaucoma.

Recently, several studies have looked at potential applications of the PAVS technique to detection and diagnosis of clinical conditions, including glaucoma (Flitcroft et al., 1996), Parkinson's disease (Troscianko and Calvert, 1993) and dementia (Cormack et al., 2004). In the former case, the authors reported that the three tests in their battery of PAVS tests successfully discriminated between patients with and without glaucoma. The intention here is to determine if those results could be substantiated, to evaluate PAVS efficiency in suspects without established conventional field loss, and to provide a cut-off point for normality across all tasks.

11.3 Method

(a) *Apparatus & Stimuli*

The apparatus and stimuli used were as described in chapter 6.

(b) *Subjects*

All subjects were required to have minimum visual acuity of 6/12 or equivalent, no significant media opacity, no other ocular or systemic disease, an open anterior chamber angle and a Humphrey visual field assessment performed within the past six

months. Subjects were then classified into one of three groups using strict entry criteria (Table 11a).

GLAUCOMA	GLAUCOMA SUSPECT	NORMAL
Characteristic ONH/RNFL damage	Suspicious ONH/RNFL structure	Normal ONH & RNFL structure. CD ratio < 0.7
Characteristic, repeatable, glaucomatous VF loss (Abnormal GHT and/or corrected pattern standard deviation < 5%, and/or cluster criteria defect*	No repeatable characteristic VF loss	Normal VF sensitivity
Classified based on IOP and gonioscopy findings		Normal intraocular pressure (IOP)
		Normal anterior chamber angle

* 3 (non-edge) contiguous pathological points, one of which at the p<1% level

Table 11a: Subject classification criteria

A total of 123 subjects were examined, 41 in each category. Glaucoma subjects ranged in age from 49 years to 83 years, with a mean age of 67 years. Suspects ranged from 44 years to 83 years, with a mean age of 62 years. Normal subjects ranged from 49 years to 83 years, with a mean age of 64 years. Normal subjects were examined and classified as such by the author. All suspect and glaucoma subjects were patients routinely attending the Mater Misericordiae hospital glaucoma clinic directed by Prof. Colm O' Brien. Glaucoma was sub-classified into normal tension (NTG), primary open angle (POAG) and secondary pseudoexfoliative (PXG) on the basis of the IOP at the time of diagnosis and the gonioscopic evaluation of the anterior chamber angle by resident Ophthalmologists in the glaucoma clinic. Subjects not meeting the criteria or not easily classified into the above categories were not included in the study.

(c) *Procedure*

The basic procedure was as described in section 6.3. All subjects were permitted 20 trial presentations for each target type, giving a total of 60 practice presentations. Each subject was required to be able to read a line of print on the screen from the correct fixation distance, each letter subtending half the visual angle of the test targets. Following the practice session, the subject began the test proper, firstly for the flicker target, followed by the displacement and then finally for the orientation target, through their near optical prescription if any (modified for the fixation distance where necessary). Each PAVS test consisted of 40 presentations of each target type.

Subjects subsequently performed a simple reaction time test followed by a choice reaction time test (Figure 6.4) to test for any non-glaucomatous motor/neural deficiencies that could complicate any interpretation of the response times observed. Each SRT and CRT test consisted of 10 presentations.

11.4 Results

(A) – GLAUCOMA Vs SUSPECTS Vs NORMALS

Table 11b shows the mean PAVS times for each subject group on each task. The data are also shown graphically in Figure 11.1 (includes the standard deviation values).

Table 11b illustrates a number of significant findings. There is an apparent increase in PAVS times among suspects and particularly in glaucoma compared to the normals group for each PAVS task. The SRT and CRT are similar between normals and suspects, but slightly increased for glaucoma. The orientation task appears to be the most difficult task for each group.

	Flicker RT	Displacement RT	Orientation RT	SRT	CRT
Glaucoma	1.17	1.15	1.96	0.53	0.66
Suspects	0.68	0.65	0.87	0.47	0.58
Normals	0.61	0.57	0.77	0.49	0.60

Table 11b: Group mean SRT, CRT and PAVS response times among *normals, suspects and glaucoma subjects*

Figure 11.1 illustrates clearly the level of difference in PAVS efficiency between the three groups. 2-tailed independent samples T test was used to compare the mean response times for each target type across the three groups (results shown in Table 11c).

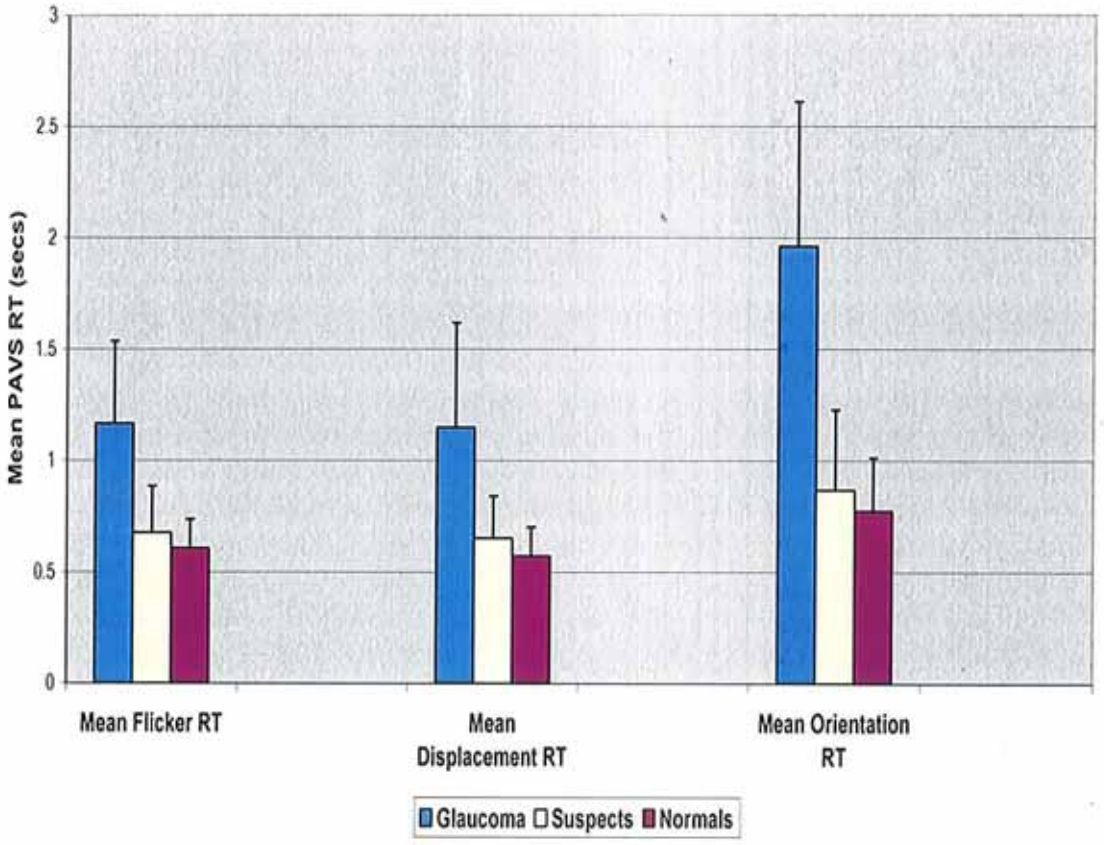


Figure 11.1: Mean PAVS response times (+ st. dev error bar) for normals, suspects and glaucoma subjects for flicker, displacement and orientation targets.

Table 11c reveals a statistically significant difference between glaucoma subjects and both normals and suspects across all PAVS targets and interestingly, also for both SRT and CRT. Differences between suspects and normals are non-significant for the flicker and orientation task, but statistically significant for the displacement task. No differences were detected in either SRT or CRT means between normals and suspects.

	Flicker	Displacement	Orientation	SRT	CRT
Glaucoma Vs Suspect	T = 7.43 P < 0.001 dF= 63.82	T = 6.25 P < 0.001 dF= 80	T = 9.34 P < 0.001 dF= 63.26	T = 4.12 P < 0.001 dF= 80	T = 3.78 P < 0.001 dF= 80
Glaucoma Vs Normal	T = 9.16 P < 0.001 dF= 51.011	T = 7.54 P < 0.001 dF= 46.251	T = 10.96 P < 0.001 dF= 50.395	T = 2.52 P = 0.014 dF= 80	T = 2.35 P = 0.021 dF= 80
Suspect Vs Normal	T = 1.76 P = 0.083 dF= 68.79	T = 2.18 P = 0.032 dF= 71.04	T = 1.39 P = 0.168 dF= 68.19	T = -0.85 P = 0.399 dF= 80	T = -0.95 P = 0.343 dF= 80

Table 11c: 2-tailed Independent samples T test for equality of PAVS, SRT and CRT mean response times, across normals, suspects and glaucoma subjects

Given the potential for variable non-glaucomatous sensory and attentional(decisional) effects on response time and the observed statistically significant difference between the CRT for glaucoma and both suspects and normals, it seemed appropriate to examine the effects of any processing differences in the statistical analysis. As such a new index was formed comprising the result of the PAVS time divided by the CRT for each subject, which we have termed the perceptual search ability (PSA).

Simple inspection of the group means of the PSA index in Table 11d again highlights a similar performance effect between the groups, with the glaucoma group mean substantially increased compared to the other groups.

	Flicker PSA	Displacement PSA	Orientation PSA
Glaucoma	1.76	1.73	2.95
Suspects	1.16	1.12	1.47
Normals	1.01	0.95	1.27

Table 11d: Mean PSA for flicker, displacement and orientation targets among *normals, suspects and glaucoma subjects*

Figure 11.2 highlights the relative PSA differences.

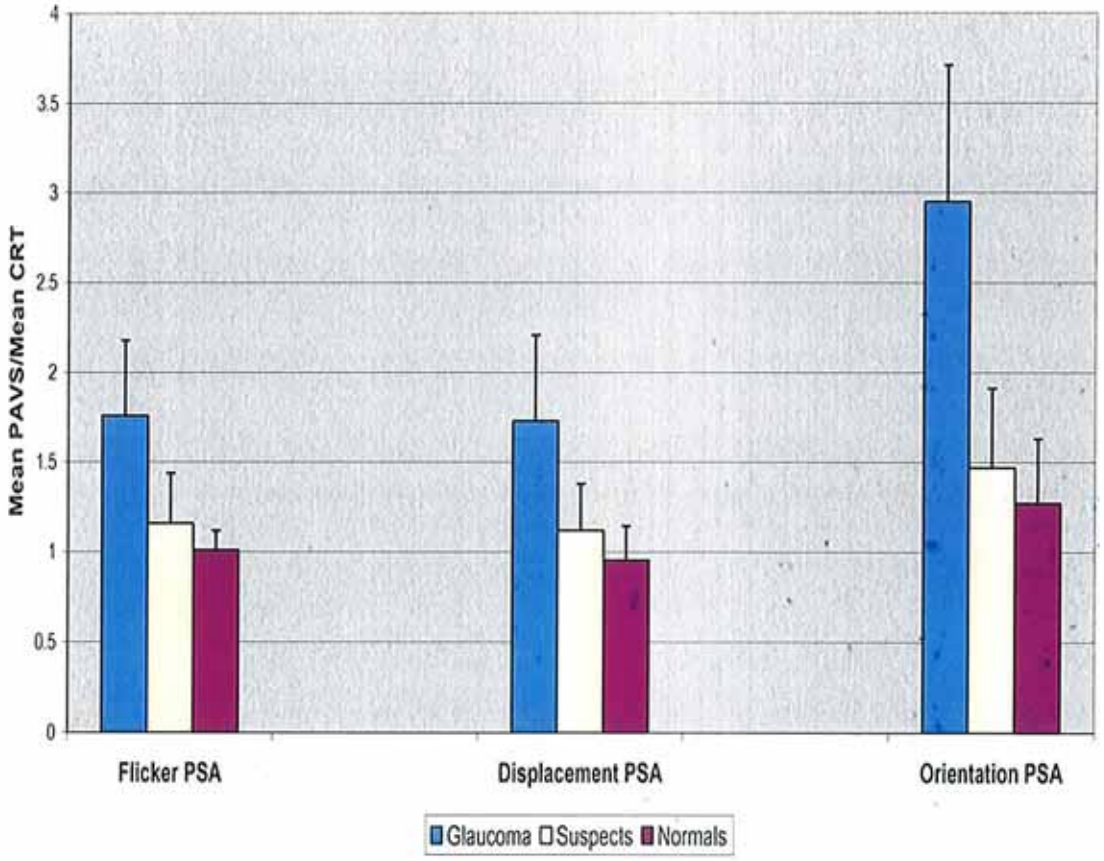


Figure 11.2: PAVS efficiency as a function of choice reaction time (CRT) - Mean PSA index (+st. dev. bars) among normals, suspects and glaucoma subjects

Independent samples T test analysis confirms the statistically significant performance impairment in the glaucoma group compared to both normals and suspects. More interestingly however, this index also appears to differentiate between the normal and suspect groups on the basis of a statistically significant difference between the respective PSA scores across all target types (see Table 11e).

	Flicker/CRT	Displacement/CRT	Orientation/CRT
Glaucoma Vs Suspect	T = 7.57 P < 0.001 dF = 69.38	T = 7.16 P < 0.001 dF= 61.75	T = 10.79 P < 0.001 dF= 64.62
Glaucoma Vs Normal	T = 10.96 P < 0.001 dF= 45.82	T = 9.96 P < 0.001 dF= 46.52	T = 13.69 P < 0.001 dF= 45.97
Suspect Vs Normal	T = 3.19 P = 0.002 dF= 53.00	T = 3.59 P = 0.001 dF= 60.62	T = 2.60 P = 0.012 dF= 56.64

Table 11e: 2-tailed Independent samples T test for equality of PSA *index* means across *normals, suspects and glaucoma subjects*

B: PRIMARY OPEN ANGLE GLAUCOMA Vs LOW-TENSION GLAUCOMA Vs PSEUDOEXFOLIATIVE GLAUCOMA

The glaucoma group was divided into three further subgroups on the basis of the IOP level at time of diagnosis, and on the status of the anterior chamber drainage angle into either primary open angle glaucoma (POAG) – 22 subjects, low tension glaucoma (LTG) – 11 subjects, or pseudoexfoliative glaucoma (PXG) – 8 subjects. The data within the glaucoma group was reanalysed to determine any possible effect of glaucoma type on PAVS efficiency.

	Flicker RT	Displacement RT	Orientation RT	SRT	CRT
POAG	1.24	1.24	2.16	0.53	0.68
LTG	1.08	1.03	1.69	0.54	0.67
PXF	1.08	1.06	1.79	0.49	0.60

Table 11f: Mean PAVS response times, mean simple reaction times (SRT) and mean choice reaction times (CRT) among *glaucoma subtypes*

Table 11f shows the POAG group to have slightly increased mean PAVS times compared to PXF and LTG for each task. LTG and PXF search efficiency appears similar in all cases (see Figure 11.3).

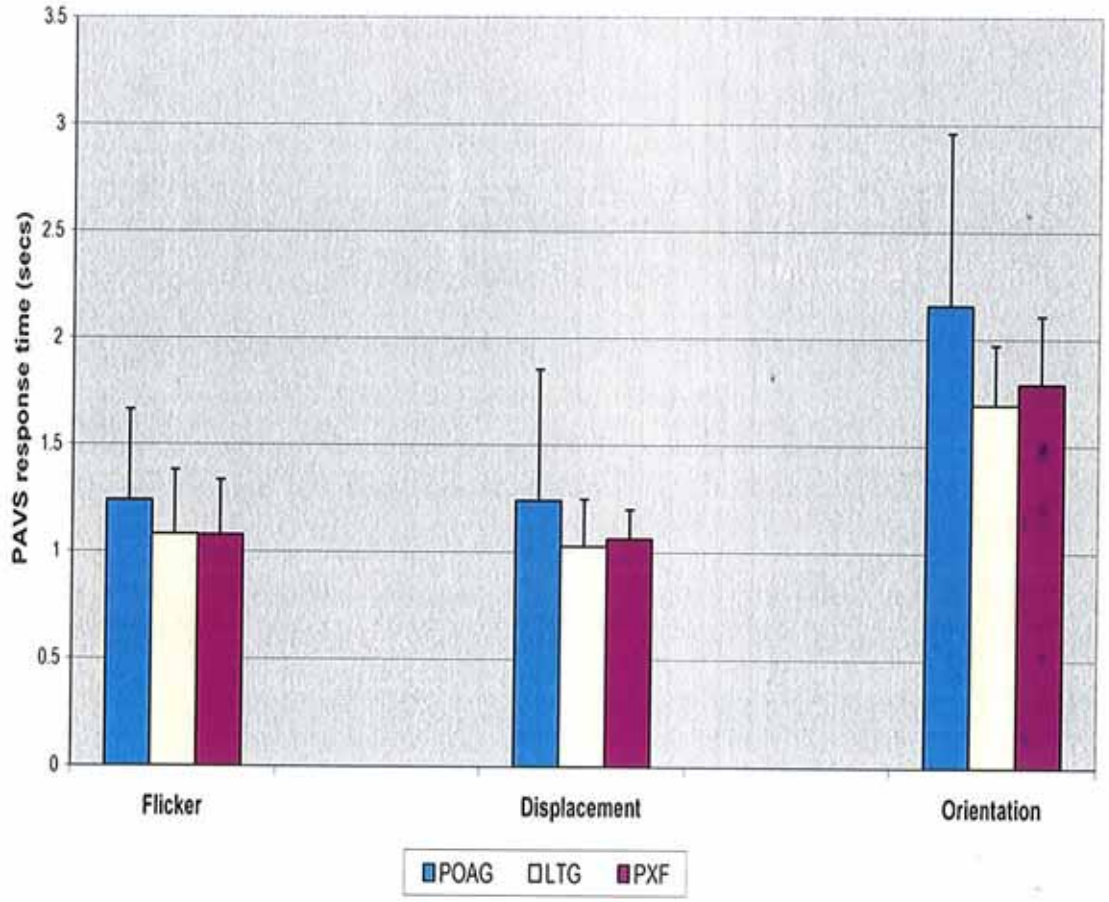


Figure 11.3: Relationship between *glaucoma subtype* and PAVS efficiency for flicker, displacement and orientation targets (Mean PAVS time + st. dev. error bars).

Table 11g charts the results of the Independent samples T test. Statistical analysis reveals no difference in PAVS efficiency between any of the glaucoma subtypes tested. Similarly, no differences were detected in either SRT or CRT means between any of the glaucoma subtypes. Even so, given the results obtained in section A when the PSA data were computed, it seemed appropriate to assess for similar effects here.

	Flicker	Displacement	Orientation	SRT	CRT
POAG Vs LTG	T = 1.11 P = 0.28 dF= 31	T = 1.11 P = 0.27 dF= 31	T = 1.84 P = 0.08 dF= 28.79	T = -0.26 P = 0.79 dF= 31	T = 0.17 P = 0.87 dF= 31
POAG Vs PXF	T = 1.01 P = 0.32 dF= 28	T = 0.80 P = 0.43 dF= 28	T = 1.24 P = 0.09 dF= 27.63	T = 1.51 P = 0.14 dF= 28	T = 1.69 P = 0.10 dF= 28
LTG Vs PXF	T = 0.03 P = 0.98 dF= 17	T = -0.41 P = 0.69 dF= 17	T = -0.706 P = 0.49 dF= 17	T = 1.779 P = 0.09 dF= 17	T = 2.096 P = 0.05 dF= 17

Table 11g: 2-tailed Independent samples T test for equality of PAVS, SRT and CRT mean response times among glaucoma subtypes

Both Table 11h and Figure 11.4 show an interesting PSA variation from the basic PAVS data above. The LTG PSA means are consistently lower than the PXF and POAG groups which are remarkably similar. The effect is largest for the orientation task.

	Flicker/CRT	Displacement/CRT	Orientation/CRT
POAG	1.81	1.80	3.14
LTG	1.61	1.54	2.53
PXF	1.80	1.79	3.01

Table 11h: Mean PSA Index for flicker, displacement and orientation targets among glaucoma subtypes

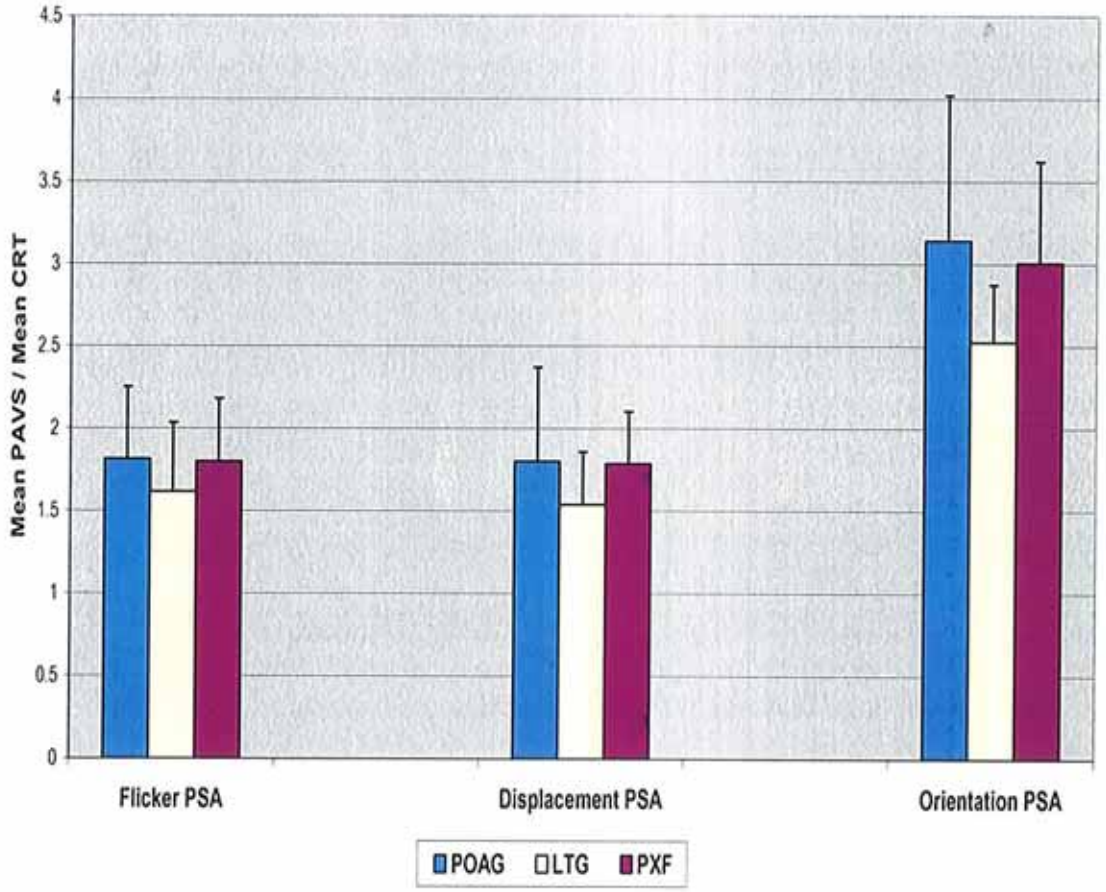


Figure 11.4: PAVS efficiency as a function of choice reaction time (CRT) – mean PSA index (+st. dev. error bars) across glaucoma subtypes

Independent samples T test confirms similar performance effects between the POAG and PXF groups across all tasks. Again there are no significant differences between LTG and both other groups for the flicker and displacement tasks. The orientation task

however shows a statistically significant difference between LTG and both POAG and PXF (Table 11i).

	Flicker PSA	Displacement PSA	Orientation PSA
POAG Vs LTG	T = 1.24 P = 0.23 dF= 31	T = 1.41 P = 0.17 dF= 31	T = 2.22 P = 0.03 dF= 29.99
POAG Vs PXF	T = 0.09 P = 0.93 dF= 28	T = 0.06 P = 0.96 dF= 28	T = 0.40 P = 0.69 dF= 28
LTG Vs PXF	T = -0.97 P = 0.34 dF= 17	T = -1.70 P = 0.11 dF= 17	T = -2.17 P = 0.044 dF= 17

Table 11i: 2-tailed Independent samples T test for equality of PSA *index* means across *glaucoma subtypes*

Having determined that the test has the capacity to differentiate normals from glaucoma, ROC curves were used to determine the optimal differentiating cut-off values for both PSA and PAVS results for each target type.

The statistics software (Stats Direct) plotted sensitivity vs. 1 – specificity for a series of cut-off values. Figure 11.5 confirms the high diagnostic capacity of the test. Area under the ROC curve (Wilcoxon estimate) is 0.987 corresponding to a sensitivity of 95.12% and specificity of 100%. The optimum PSA cut-off for normality for flicker was determined to be = 1.281 (point marked "o" in Figure 11.5).

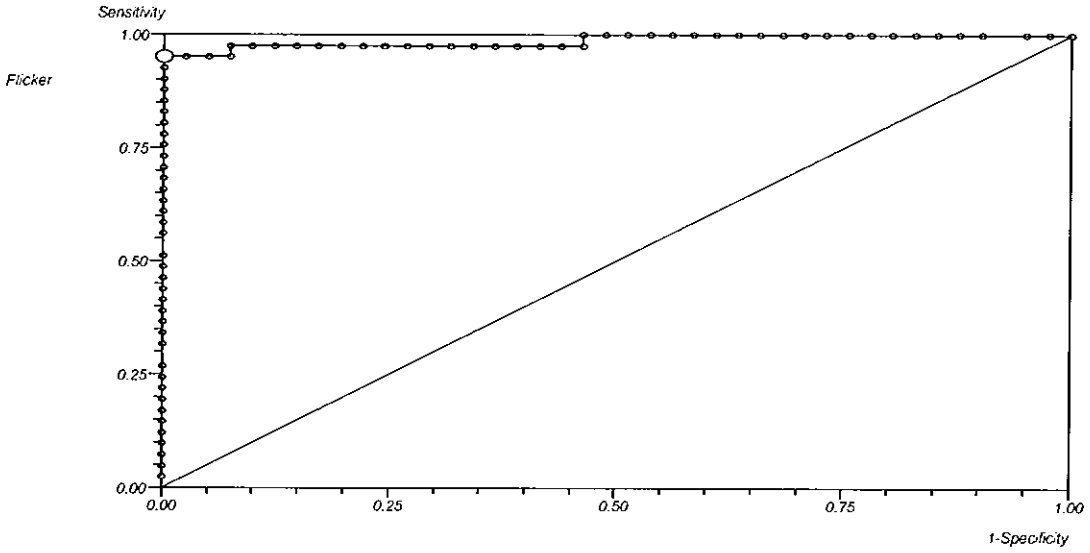


Figure 11.5: ROC curve for flicker PSA, results of normal controls versus glaucoma subjects.

Area under the ROC curve in Figure 11.6 (Wilcoxon estimate) is 0.980 corresponding to a sensitivity of 95.12% and specificity of 95.12%. The optimum PSA cut-off for normality for displacement was determined to be = 1.195.

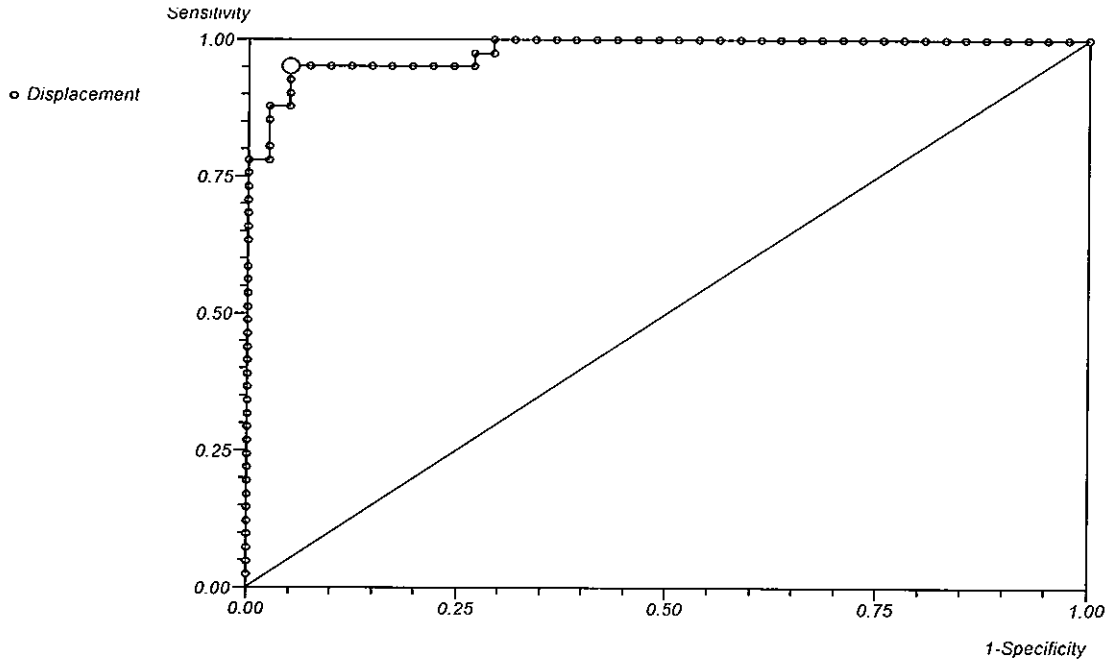


Figure 11.6: **ROC curve for displacement PSA, results of normal controls versus glaucoma subjects.**

Area under the ROC curve in Figure 11.7 (Wilcoxon estimate) is 0.997 corresponding to a sensitivity of 99.70% and specificity of 99.16%. The optimum PSA cut-off for normality for orientation was determined to be < 1.897.

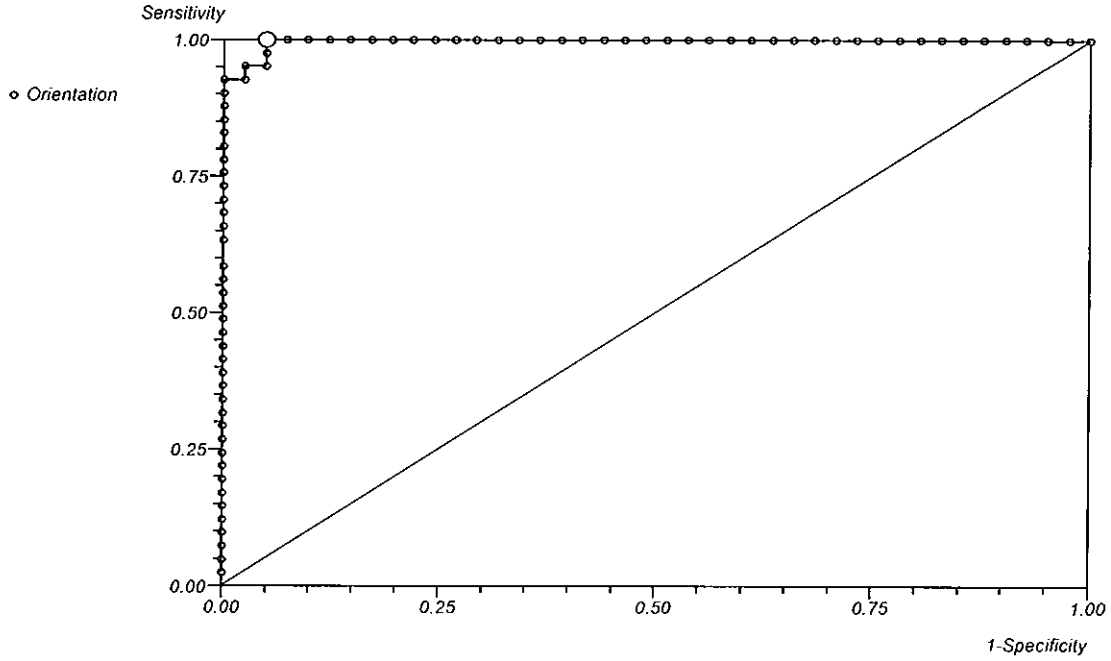


Figure 11.7: **ROC curve for orientation PSA, results of normal controls versus glaucoma subjects.**

Similar analysis of the PAVS data confirms the sensitivity and specificity of the test remains high. Area under the ROC curve in Figure 11.8 (Wilcoxon estimate) is 0.971 corresponding to a sensitivity of 92.68% and specificity of 90.24%. The optimum PAVS cut-off for flicker normality is < 0.81 seconds.

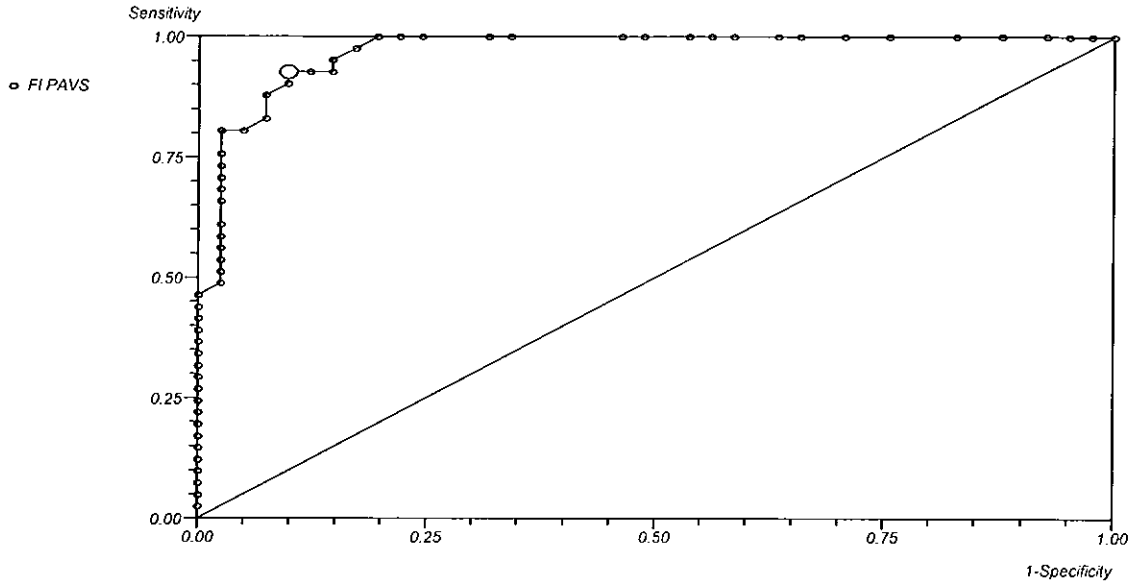


Figure 11.8: **ROC curve for flicker PAVS, results of normal controls versus glaucoma subjects.**

Area under the ROC curve in Figure 11.9 (Wilcoxon estimate) is 0.974 corresponding to a sensitivity of 90.24% and specificity of 95.12%. The optimum PAVS cut-off for normality for displacement is < 0.83 seconds.

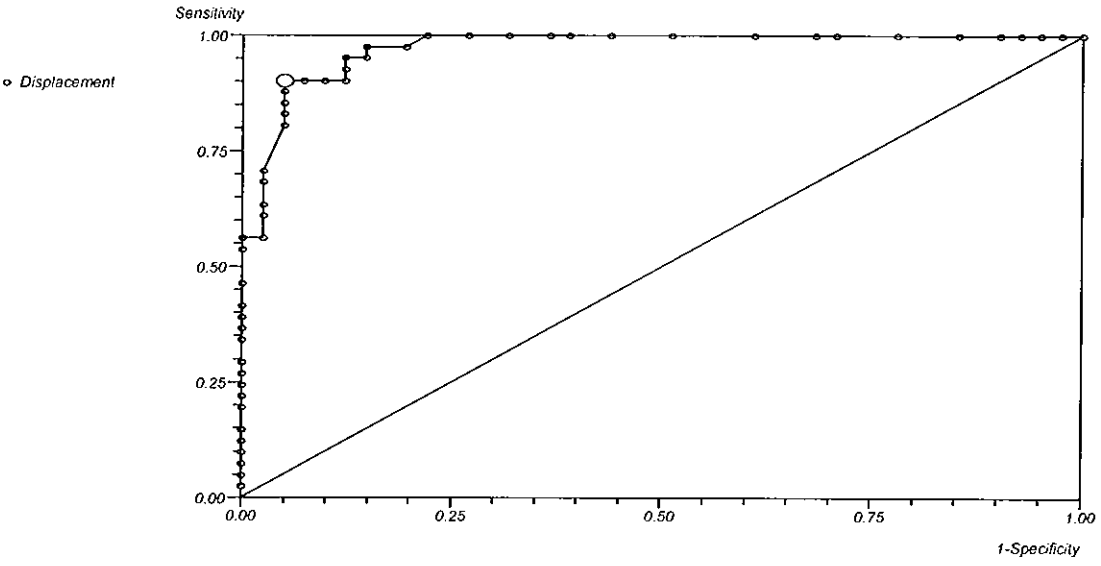


Figure 11.9: **ROC curve for displacement PAVS, results of normal controls versus glaucoma subjects.**

Area under the ROC curve in Figure 11.10 (Wilcoxon estimate) is 0.987 corresponding to a sensitivity of 91.39% and specificity of 92.68%. The optimum PAVS cut-off for normality for orientation is < 1.20 seconds.

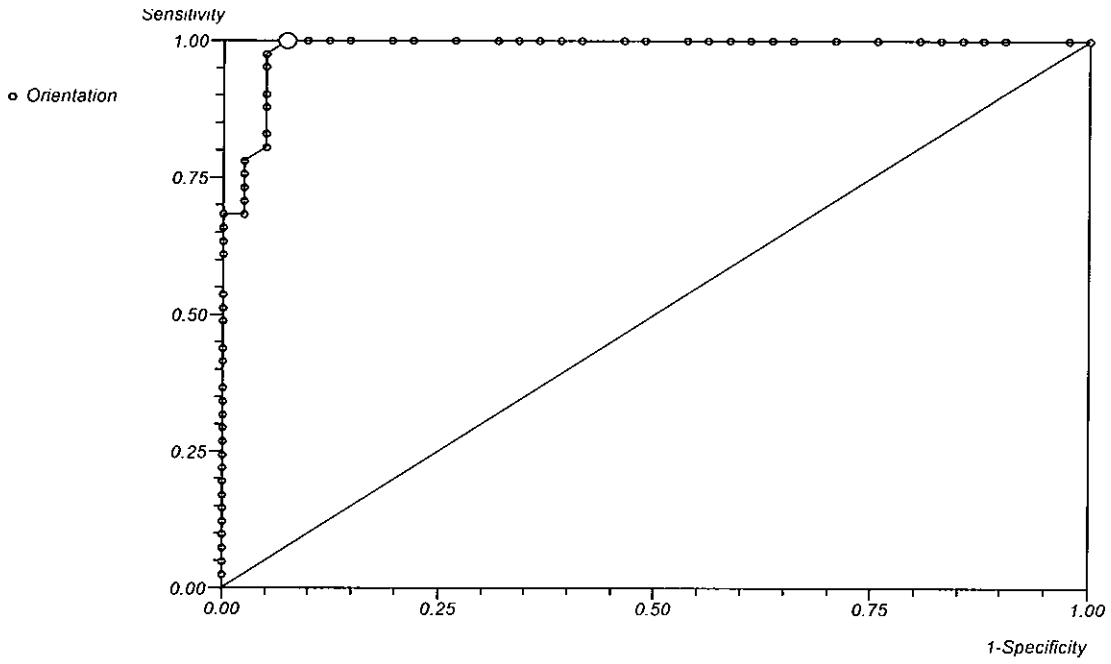


Figure 11.10: **ROC curve for orientation PAVS, results of normal controls versus glaucoma subjects.**

Table 11j provides a list of sensitivity and specificity values obtained for each task and illustrates that for all target types, test sensitivity and specificity remains highest when the PSA index is employed rather than the raw PAVS values, confirming the merit of producing such an index. The "sensitivity x specificity" index in Table 11j shows the orientation PSA task to yield the most accurate discrimination between groups.

	PAVS Flicker	PAVS Displacement	PAVS Orientation	PSA Flicker	PSA Displacement	PSA Orientation
Sensitivity	92.68%	90.24%	91.39%	95.12%	95.12%	99.7%
Specificity	90.24%	95.12%	92.68%	100%	95.12%	99.16%
Sensitivity x Specificity	8363.44	8583.63	8470.03	9512	9047.81	9886.25 *

Table 11j: Sensitivity and specificity scores for each task and sensitivity x specificity scores indicating relative discrimination capacity (*most diagnostic)

11.5 Discussion

The nature of the various target/distractor design combinations here is such as to create a test with the potential to stimulate (at least preferentially, if not exclusively) and assess the integrity of different ganglion cell populations within a single examination. The temporal characteristics of the flicker and motion displacement targets used here naturally stimulate the fast conducting magnocellular pathway. The high spatial frequency, stationary orientation target/distractor combination will be preferentially coded by the sustained parvocellular pathway. It is therefore unsurprising that the orientation task employed here has consistently increased PAVS response times compared to the flicker and motion targets.

This may reflect a difference in the processing speed of the two pathways involved, a fundamental difference in the processing capacity of the two pathways, a difference in the capacity for attentional capture of a stationary versus a motion/flicker singularity

(moving targets may be visually more important from an evolutionary perspective), or possibly nothing more than a basic difference in the task complexity.

Nonetheless all three targets appear to have the capacity to differentiate glaucoma from non-glaucoma on the basis of preattentive search efficiency. Our results confirm that subjects with established early glaucoma have impaired parallel search capabilities when compared to either age-matched normal subjects or glaucoma suspects without established visual field loss. The degree of impairment was highly statistically significant for each target type. This is a highly important finding as it suggests that PAVS/PSA is potentially a more sensitive indicator of the presence of glaucoma than conventional achromatic perimetry, which by definition, finds no characteristic difference in sensitivity between glaucoma patients and suspects.

The use of a reaction time paradigm instead of a thresholding strategy has significant benefits with regards to task simplicity and speed. It does however leave interpretation of data based solely on a subjects speed of response open to misdiagnosis were a subjects response time artificially increased due to non-visual functional deficits. For example, a subject with severe chronic rheumatoid arthritis could conceivably have significantly increased response times due solely to poor manual dexterity in the absence of any loss of preattentive visual search efficiency. Other neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and dementia with Lewy bodies (indeed a suggested link between such neuro-degenerations and glaucoma has been cited – Pache & Flammer, 2006) have been shown to cause significant variability in attentional performance and fluctuations in awareness capable of influencing response time strategies (Ballard et al., 2001). Chapter 8 gives a comprehensive review of the additional sensory and attentional cognitive effects on response time paradigms

associated with older age groups. The SRT and in particular, the CRT test results are therefore important diagnostic tools in the overall interpretation of results.

The SRT test evaluates a subject's ability to simply react to the sudden appearance of a target on screen. It requires no complex processing or top-down search decisions and is designed therefore to elucidate any loss of response time speed due to any physical or non-visual neural processing limitations.

The CRT test requires a subject to indicate the location of a specific target with only one distractor. As such it represents a quite primitive search task. If preattentive search efficiency is compromised, a decision can still be made following a rapid saccade at stimulus onset to one of two possible locations. A decision on target location can thus be made almost instantaneously. By its very nature, preattentive search times should not increase significantly above the CRT regardless of the number of distractors. The CRT therefore gives an indication as to the approximate PAVS time a subject should achieve given normal preattentive processing skills.

The CRT was thus used to determine an alternative performance index (perceptual search ability – PSA), presumed to be free of any such potential artifactual defects. The PSA index thus provides a more robust indication of performance efficiency.

The PSA index analysis confirms the loss of search efficiency in the glaucoma group to be statistically significant. The finding that the suspect group PSA data is significantly different from the normal group data is of particular importance. The magnitude of the effect is obviously lower than that observed in the glaucoma group, reflecting perhaps the fact that neural loss is, by definition, more advanced in the

glaucoma group. The PSA index is on average 15 – 17% higher for suspects compared to normals depending on target type, and between 76% (flicker) and 230% (orientation) increased for glaucoma above normal. While the current results are not sufficient to say that the test is capable of defining those patients classified as suspects most likely to develop glaucomatous field loss, they are however encouraging enough to suggest that a longitudinal analysis of such patients might be worthwhile to determine if those with the largest PSA values are those who progress. A test that can determine those most at risk is of developing glaucoma is of obvious merit.

ROC curve analysis confirmed the high sensitivity and specificity of both the PAVS and PSA data in the diagnosis of glaucoma. PSA retains marginally increased sensitivity and specificity over PAVS across each target group indicating that it may provide a slightly better performance index. Table 11k gives details of the optimum cut-off values as determined by the analysis.

	Flicker	**Displacement**	**Orientation**
Optimum PSA	**1.281**	**1.195**	**1.897**
Optimum PAVS	**0.81s**	**0.83s**	**1.20s**

Table 11k: Task specific normal cut-off values for PAVS and PSA

Differentiating normals from glaucoma is an important factor in determining the clinical value of the test. Equally important however is the identification of those patients classified as glaucoma suspects most likely to develop glaucoma. While longitudinal analysis is essential to determine the tests capacity to successfully identify such patients, comparison of the raw suspect data with the determined optimal cut-offs above might give some indication as to those suspects most likely to progress. Such

analysis reveals that for the flicker task, 11 of the 41 suspects exceeded the normal criterion for PSA, and 9 for PAVS (8 of whom failed on both counts). For displacement, 10 suspects exceeded the criterion for PSA and 7 for PAVS (all 7 also failed the PSA index criterion). For orientation, 6 suspects exceeded the criterion for PSA and 7 for PAVS (includes the same 6 PSA fails). In total 11 suspects exceed the maximum normal value for PAVS on at least one of the three tasks, and 14 exceeded the normal PSA maximum on at least one test. Four suspects met the glaucoma criterion on both PSA and PAVS for all three tasks. Interpretation of these results might suggest that at least some of these subjects have definite functional loss that may eventually progress to an established glaucomatous visual field defect.

Glaucoma is a multifactorial condition with numerous suggested aetiologies. The relative contributions of mechanical deformation, vascular insufficiency and neurotoxic injury have been reviewed in chapter 4. The extent of involvement of the various mechanisms may vary with the different types of glaucoma. Laminar compression may predominate in cases of elevated IOP (except possibly in association with systemic hypotension where low perfusion pressures may result in a vascular element also), while low tension glaucoma may have a predominantly vascular or atherosclerotic aetiology.

While the end result is always the same- ganglion cell death, the pattern of damage and timeframe for cell death in glaucoma may vary and as such may have different effects on PAVS performance at different stages. Analysis of PAVS efficiency among cases of POAG, LTG and PXF however does not reveal any significant differences in performance between the three glaucoma groups. The observed PSA difference for LTG compared to both POAG and PXF for the orientation target poses some

interesting questions. Search remains marginally less affected in LTG than the other two groups. Does this suggest a relative preservation of parallel mechanisms in the pathogenesis of LTG compared to other high tension cases? Is this preservation limited to or more significant in the parvocellular pathway given that the difference is statistically significant for orientation alone? One might thus hypothesize that smaller diameter parvocellular fibres are less susceptible than their magnocellular counterparts to vascular insufficiency (or whatever the cause of LTG) while the compressive effects of higher IOP are less selective for pathway (magno and parvo both affected) at this stage of glaucoma. Such a hypothesis remains to be tested.

The importance of early detection to glaucoma management and visual prognosis has been well established (Tezel et al., 2001). Evidence of (i) selective damage to large ganglion cells in the retinal mid-periphery (Quigley et al., 1987; Glovinsky et al., 1991) and at the fovea (Glovinsky et al., 1993) in human and experimental glaucoma, (ii) psychophysical losses of M cell function (Anderson & O' Brien, 1997) and (iii) observations of reduced axonal flow to the magnocellular layers of the lateral geniculate body subserving the retinal mid-periphery (Dandona et al., 1991) have led to attempts to develop tests that isolate the magnocellular pathway.

Inconsistencies (such as loss of visual functions mediated by the parvocellular pathway) in the selective cell loss hypothesis mean that selective cell death is no longer widely accepted. Instead, glaucomatous cell death is presumed to be rather non-selective. Retinal sampling has become central to the development of novel tests of retinal function in glaucoma. Cells that have sparse representation (retinal undersampling) may yield the earliest detectable losses of visual function (Johnson, 1994). The insensitivity of conventional perimetric stimuli most likely reflects the

non-selective nature of the achromatic stimuli used, and the significant degree of overlap of ganglion cell receptive fields in all retinal locations masks early functional losses.

As such the current test, which incorporates stimuli capable of testing both pathways to varying degrees, and has shown consistently high sensitivity and specificity to glaucomatous losses, may provide a useful alternative screening technique for the rapid clinical evaluation of visual functional status in those at risk of glaucoma. Longitudinal analysis should confirm its true diagnostic capacity.

CHAPTER 12

CONCLUSIONS

12.1 Conclusions

Visual search has long remained the domain of the vision psychologist, exploiting the search paradigm to more fully describe the vision processes involved in attention. Given the accepted importance of vision mechanisms in the deployment of attention, it seems logical that vision scientists and clinicians should further investigate the efficiency of visual search in conditions where behavioural patterns are affected so that visual information may not be correctly utilized, or where the initial visual information is deficient in some form, potentially degrading the efficient deployment of attention. The clinical application of visual search strategies however, particularly in conditions where the primary defect lies in retinal rather than higher level processing abnormalities remains virtually unexplored.

Previous research appears to have largely adopted stimuli and procedures similar to those used in conventional psychology (small numbers of distractors and a time/accuracy paradigm), and attempted to determine merely whether the condition under investigation affected search efficiency and to exploit the data findings to further elucidate the nature of the condition (e.g. Troscianko & Calvert, 1993; Cormack et al., 2004). These have essentially been confined to behavioural conditions such as dementia, Alzheimer's and Parkinson's disease. Such investigations are of obvious merit, but to our knowledge, while Flitcroft et al. (1996) devised the test and explored its usefulness in glaucoma, no previous attempt has been made to systematically assess a visual search test across a range of factors that may influence its clinical application in the screening for and/or diagnosis of such conditions.

To this effect, the current study represents a novel investigation into the potential of a visual search test for clinical application as a diagnostic test procedure for glaucoma.

Desirable features in a new clinical test include: (1) high sensitivity to the condition, (2) high specificity to the condition, (3) differential diagnostic efficacy, (4) high reliability and reproducibility, (5) the ability to predict which individuals at risk will actually advance to the development of the condition, (6) clinical robustness, (7) validity, (8) the ability to be easily incorporated into a clinical test environment and (9) a potential quantitative relationship to disease severity to facilitate longitudinal analysis and monitoring patient response treatment. While test sensitivity and specificity has been previously explored (Flitcroft et al., 1996), the major contributions of the current project can be summarised by assessing how the experimental methods and analyses have (a) served to evaluate the clinical viability of the test for glaucoma and (b) further contributed to the research body of evidence relating to visual search and to glaucoma.

12.2 Summary and Implications of Results

The previous paragraph outlines a most demanding set of criteria for new test development. Such criteria it appears have never previously been explored in relation to visual search in a diagnostic environment.

12.2.1 Test Sensitivity and Specificity

The most important measures include test sensitivity and specificity to glaucoma. The current data support Flitcroft et al.'s assertion that a test of PAVS can both correctly identify patients with glaucoma and also correctly distinguish normal individuals from patients with glaucoma. Using the diagnostic criterion of perceptual search ability (PSA), the test correctly distinguishes normals from glaucoma and importantly also differentiates the suspect group from normals. This would suggest that the test is capable of identifying those most likely to progress to glaucoma. ROC curve analysis

reveals sensitivity and specificity above 95% on PSA for all tasks and furthermore provides hitherto un-established normal performance cut-off values for each task which would be essential in a clinical environment. These results are proof positive that the test is useful in the evaluation of glaucoma, however, in isolation, these findings are insufficient to merit clinical placement of the test. The effect of stimulus attributes and other visual parameters required elucidation.

12.2.2 Perceptual Learning & Retinal Eccentricity Effects

The effects of perceptual learning and retinal eccentricity are known to influence search efficiency. The magnitude of such effects obviously influences the application and interpretation of clinical testing and therefore warranted investigation. The results suggest that for suprathreshold stimuli as employed here, retinal eccentricity is not a significant variable. Perceptual learning appears to saturate quickly which suggests that only a small amount of practice should be required and the persistence of learning infers that test results should prove reliable and reproducible. This is a significant finding, given the variability problems associated with traditional psychophysical techniques such as achromatic and short wavelength perimetry, a repeatable test is beneficial.

12.2.3 Age

The effect of age, which could be expected to have a pronounced effect on test interpretation, has been rendered negligible by the design of an index of perceptual search ability. To our knowledge, this represents an entirely new approach to the evaluation of search efficiency. There are many psycho-motor factors that could influence performance, and to ignore their potential impact would have serious repercussions for the clinical viability of the test. The PSA index development which

serves to heighten test sensitivity and specificity, to make the test more clinically robust and to potentially highlight the way forward for clinical use of a visual search test of visual integrity, may seem a small advancement but is perhaps the single most significant achievement of the project.

12.2.4 Optical Blur

Investigation of the effects of optical blur confirms the test to be largely independent of the potential effects of reduced visual acuity. The flicker and displacement tests remain resistant to substantial losses of acuity, while even the orientation task is resistant to at least the equivalent of up to 6/12 (~1.00D spherical ametropia). Given the population most at risk of development of glaucoma where other variables such as macular degeneration or cataract that may serve to reduce foveal acuity are most prevalent, the presumption of test robustness is further enhanced.

Our investigations therefore have allowed us to more completely assess the design structure of the test, to make suitable design enhancements and subsequently draw the conclusion that the test satisfies to a greater or lesser extent the above criteria. The current test provides a robust, highly sensitive and clinically valid alternative to established diagnostic techniques. The rapid test time, ease of use, ease of interpretation, potentially simple integration into existing clinical environments and probable comparative low-cost suggests that it is a technique that could possibly gain widespread clinical placement.

12.3 Contributions to Understanding Visual Search and Glaucoma

Glaucoma is known to cause peripheral field loss but its impact is often underestimated. The inability to detect a target in an isolated area of the visual field

may not be perceived as a significant disability. The determination here however that glaucoma adversely affects an individual's capacity to deploy attention is an important one. This can be applied to infer the potential impact of the condition on lifestyle even in the absence of diffuse perimetric field loss. Everyday tasks such as searching for car keys may prove more tedious and require more serial inspection. The ability to guide attention is a fundamental capacity of the human system and when compromised through visual dysfunction has the potential for devastating consequences.

Other significant contributions may be summarized as follows:

- Development of a PSA index provides a novel means of isolating the true visual search effects of compromised visual function by eliminating psycho-motor deficits.
- Traditionally, orientation tasks have been used in clinical PAVS tests. The current strategy utilizes for the first time flicker and motion displacement tasks that may be appropriate in the detection of glaucoma. When combined with the orientation task, the test becomes capable of preferentially assessing the parallel pathways that may be differentially affected in glaucoma, potentially increasing the diagnostic capacity of the test.
- Glaucoma results hint at a dissociation between the effects of low versus high tension glaucoma on search efficiency. Previous research suggests that the mechanism of damage and the type of perimetric field defects are different between the two types. This finding extends that interpretation to visual search although more detailed examination would be appropriate to substantiate this.
- For the first time diagnostic PSA values have been determined based on response times (RT) rather than the RT x set size slopes traditionally quoted.

Such PSA values facilitate easier clinical interpretation of results in terms with which clinicians are possibly more familiar.

- Some of the task specific findings here serve to modify the conclusions of other authors. Eccentricity effects for example are negligible here which is at odds with previous findings. The nature of the stimuli thus will play a significant role in determining the presence or absence of such an eccentricity effect. The suprathreshold nature of the stimuli employed here negates the effect. The effect of blur was previously untested, and while the resistance of flicker to blur in other psychophysical techniques had been established (see chapter 7) the results here substantiate its resistance in visual search. The results of such ametropia effects have been published (Loughman & Davison, 2002; Davison & Loughman, 2006).

Early and accurate diagnosis of glaucoma is imperative to optimise clinical management. Whether the current test detects pre-perimetric field loss is yet to be established and therefore its ultimate value remains to be seen. What is presently obvious is its significant, raw potential as a mass screening tool for glaucoma with sensitivity and specificity values vastly in excess of tonometry or ophthalmoscopy. Evaluation in other clinical optic neuropathies may also serve to widen its scope of practice and yield a valuable tool in the investigation of ocular dysfunction.

12.4 Future Research

The field of visual search, in particular the clinical application of search tasks for the detection of conditions affecting the eye and vision, remains relatively young and very much in the developmental stages. As such there remains significant scope to enhance and explore its suitability in various ocular and neurological conditions. The current

project has also served to highlight the need for future research in certain areas to further elucidate both its diagnostic capacity and its scope of clinical practise. The following investigations would prove valuable:

- **Longitudinal Analysis of Glaucoma Suspects**

The results in chapter 11 suggest that when the PSA scores are evaluated, the current search tasks differentiate between suspects and normals as a group. Comparison with cut-off values determined through ROC curve analysis also highlights those suspects within the group with PSA scores most similar to that observed in the glaucoma group. This suggests that the battery of tests employed here may be more sensitive than conventional achromatic perimetry. To confirm whether this is truly the case however requires longitudinal evaluation of the suspect group. Regular evaluation of both perimetric and visual search performance may provide some indication as to whether the test correctly identifies those suspects most likely to progress to established glaucomatous field loss. Accurate identification of such patients would add significant value to the test. What currently exists is a rapid and accurate screening test, such additional capacity would potentially provide an additional means to facilitate and steer treatment decisions.

- **Longitudinal Analysis of Established Glaucoma**

The role of any test in the investigation of glaucoma is not merely to initially detect the condition but it should also serve to monitor the status of the condition and principally prove capable of detecting change or progression in the extent of functional damage caused. Failure to do so would diminish the clinical usefulness of the test once glaucoma has been established. As such further longitudinal analysis of search performance among (i) the current group of glaucoma patients, (ii) among patients

known to have progressive neuropathy despite treatment and (iii) among glaucoma patients in various stages of the condition is essential to determine whether a relationship exists between the extent of damage and the level of PAVS performance. Anecdotally, a relationship does appear to exist in that patients with advanced field loss find the tasks virtually impossible to complete within the 5 second timeframe allowed to detect a target. The nature of such a relationship needs evaluation.

- **Comparison of Search Performance with Visual Field Loss**

The results from the glaucoma group outlined in chapter 11 demonstrate a broad range of PSA scores among patients with essentially similar amounts of field loss. Flicker PSA ranges from 1.03 to 3.1, displacement from 0.98 to 3.73 and orientation from 1.89 to 4.96. This finding poses some interesting questions. How does visual search performance correlate with incremental light sensitivity? Do patients with similar amounts of field loss actually have a broad range of functional loss not distinguishable by conventional perimetry? How do the various types of field loss (different quadrants/hemispheres, paracentral versus more peripheral losses etc.) influence visual search performance? Can visual search results predict the most likely location of a future field defect in a glaucoma suspect? The answers to these questions and more can be found through specific comparisons and would provide further information as to the nature of the functional losses in glaucoma.

- **Ocular Blood Flow Analysis and Visual Search**

As outlined in chapter 4 ocular blood flow has been shown to be a causative factor in primary open angle glaucoma. In particular, cases of low-tension glaucoma are presumed to have a vascular origin due to the presence of "normal" IOP, disc haemorrhages, vasospastic disease (Drance et al., 1988) and other vascular

abnormalities (e.g. Leibovitch et al. 2005). The results here suggest that perceptual search ability is somewhat less affected in LTG. It would indeed be interesting to assess ocular blood flow in cases of low and high tension glaucoma and attempt to correlate such findings with visual search performance in both groups. Further analysis could include tests to evaluate the integrity of the magnocellular and parvocellular pathways independently such as through SWAP (parvo) and frequency doubling (magno) to assess whether the statistically significant preservation of search performance on the parvocellular orientation task reported in chapter 11 can be replicated and expanded using other psychophysical tests.

- **Future Test Design Enhancement**

Two distinct developmental opportunities exist for future test enhancements. The more immediate aspect relates to the application of the test in a clinical environment as a screening tool initially. The developments required include:

- Interpretation of the test results is still unsatisfactory in its current format. There is currently no indication given as to whether the test results are normal or not (because normal values were previously unknown). The data display sheet needs to incorporate the current cut-off normal values and provide an index of normality for the clinician. Perhaps the logical approach would be to adopt a printout similar to that used in perimetry which would be readily understood by clinicians, with a plot of PAVS and/or PSA values across field locations, perhaps a greyscale plot for patient benefit, and a generic index derived from a normative database to describe the performance level achieved (e.g. similar to the GHT analysis of the Humphrey VFA using "outside normal limits", or the nerve fibre indicator (NFI) numeric index provided by the GDx).

A more expansive normative database needs to be applied so that such a generic index proves clinically robust.

- The rate of flicker used here was 16Hz for all experimental paradigms. This should be sufficient to have preferentially stimulated the magnocellular pathway. However the rate of flicker could be adjusted to determine whether a higher rate of flicker (perhaps up to 32Hz) improves the diagnostic capacity of this task by further dampening the response potential of the parvocellular pathway. Given its already high diagnostic capacity, this is perhaps not an overly important investigation but nonetheless could provide some interesting results.
- The orientation task remains the most difficult search task employed here (although it has been shown to have the highest diagnostic capacity). It might prove beneficial to explore other target/distractor designs in an attempt to reduce the complexity of the task. The stimuli used are both familiar shapes (**N** and **Z** or + and **x**). Given the asymmetries reported in visual search tasks and the role of familiarity in feature discriminability (Wolfe, 2001), perhaps alternative orientation designs might make the test somewhat easier and faster to complete. An obvious candidate would be to explore the potential of feature presence versus feature absence (see Figure 2.18 for an example) rather than just feature differences. If the test proves easier (and/or more robust) without diminishing its diagnostic capacity then the investigation would be of obvious merit.
- An important statistical tool in the assessment of the performance of a test in clinical conditions would be the randomisation of the order of task completion. Unfortunately the test as it currently stands does not permit such random presentation order. While we would contend that the non-randomisation did not

significantly affect the results or our interpretation of the results where it was absent, it is nonetheless a significant variable that could potentially mask certain task effects. One could for example, suggest that the orientation task was potentially the most diagnostic for glaucoma merely because it was the last test performed. The fact that flicker (the first test) was more diagnostic than displacement could counteract such a suggestion. It would be beneficial that the test is enhanced to permit such randomisation for any future investigations.

The second test design strategy represents a more long term goal to incorporate current and pipeline software and hardware strategies with more extensive capabilities than the existing basic software program. One of the principal benefits of the existing test is the ease with which it could be incorporated into routine clinical practise and while sight of this should not be lost, there exists opportunities to develop experimental strategies to more adequately assess visual function. Indeed the test would benefit from the increased transportability that rewriting the software using web-based languages such as Javascript or other alternatives could offer.

It is a strongly held personal belief that current psychophysical strategies which use artificial stimuli ranging from Gabor patches and sinusoidal gratings to lines and spots of light, while useful for describing visual attributes, are perhaps not the ideal means of assessing visual performance in a real world environment. As a clinician I am occasionally intrigued by patient complaints about their visual sensation in the absence of definable abnormalities and have come to the conclusion that our investigative techniques cannot fully describe real world effects of ocular disease.

Visual search, a strategy employed ever more in our cluttered social, work and home environments represents a significant opportunity to explore visual performance in environments adopting naturalistic stimuli and where performance is not restricted by the absence of eye or head movements. Current search paradigms utilise computer generated stimuli which are also less than ideal. It is impossible to replicate the wide range of conditions including colour, background and target luminance, motion and distractions among others, that impact on our visual performance using such stimuli and system designs.

Virtual reality systems however hold the potential to interactively exploit more realistic stimuli. The main advantage of using immersive virtual reality is that the observer can explore their environment freely, while appropriate images are generated for each eye just as if they were viewing a real scene. Virtual reality systems have already been used to attempt to more completely describe visual perception (e.g. Glennerster et al., 2006) and visual search (Flanagan et al, 1998) and also to attempt to provide some means of restoring visual function in cases of eye disease (e.g. Viirre et al., 1998). To my knowledge no attempt has yet been made to adopt such technology for the diagnosis of ocular disease and/or more completely describe a disease process. Immersive virtual reality technology represents an exciting and potentially important tool in the exploration of vision.

- **Visual Search in other Ocular Conditions**

There is also the opportunity of exploring (i) the effect of other ocular abnormalities on visual search and (ii) the usefulness of visual search in the diagnosis of other ocular conditions.

(i) Optical defocus has been shown to affect search performance for orientation. This could be extended to elucidate the effect of other sources of sensory image degradation such as cataract and macular degeneration and cortical deficits such as in amblyopia.

(ii) Other optic neuropathies also merit investigation using visual search techniques. Optic neuritis for example is an obvious candidate where demyelinating disease and the associated visual loss and conduction abnormalities may affect search performance.

In conclusion, a suitably configured visual search strategy, in exploring a fundamental capacity of the visual system incorporating numerous visual attributes, possesses vast, largely untapped potential to both describe and detect abnormality in visual function. The current project has examined and provided answers to a number of important questions but there remains significant scope for future investigations.

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Appendix 1 – Consent Form

Researcher's Name: (use block capitals) DR PETER DAVISON & JAMES LOUGHMAN	**Title:**
Faculty/School/Department: SCIENCE/PHYSICS/OPTOMETRY	
Title of Study: INVESTIGATIONS OF PRE-ATTENTIVE VISUAL SEARCH	
To be completed by the: **subject~~/patient/volunteer/informant/interviewee/parent/guardian~~** *(delete as necessary)*	

3.1 Have you been fully informed/read the information sheet about this study? YES/NO

3.2 Have you had an opportunity to ask questions and discuss this study? YES/NO

3.3. Have you received satisfactory answers to all your questions? YES/NO

3.4 Have you received enough information about this study and any associated health and safety implications if applicable? YES/NO

3.5 Do you understand that you are free to withdraw from this study?

- at any time
- without giving a reason for withdrawing
- without affecting your future relationship with the Institute YES/NO

3.6 Do you agree to take part in this study the results of which are likely to be published? YES/NO

3.7 Have you been informed that this consent form shall be kept in the confidence of the researcher? YES/NO

Signed_____ Date _____

Name in Block Letters _____

Signature of Researcher _____ Date _____

Please note:

- For persons under 18 years of age the consent of the parents or guardians must be obtained or an explanation given to the Research Ethics Committee and the assent of the child/young person should be obtained to the degree possible dependent on the age of the child/young person. **Please complete the Consent Form (section 4) for Research Involving 'Less Powerful' Subjects or Those Under 18 Yrs.**

- In some studies, witnessed consent may be appropriate.

- The researcher concerned must sign the consent form after having explained the project to the subject and after having answered his/her questions about the project.

Appendix 2 – Patient Information Sheet

Study Background:

The current study is designed to evaluate the potential of a novel test to become a clinical test for the detection of glaucoma. To this effect numerous linked investigations are ongoing. The objective of this study is to improve our knowledge of "preattentive vision" and use the results to test for eye diseases.

What to Expect:

- Details about your general health, past ocular history and family history are important and will be requested prior to test completion.
- The standard of your vision and the status of your ocular health will also be examined using routine equipment and techniques
- Unless otherwise specified, the investigation will not require the use of any diagnostic drugs. Where required, the nature, rationale for use, precautions and potential side effects of such drugs will be thoroughly explained. Otherwise the study does not involve any contact with the eye or have any associated risks.
- The results and findings of the investigations may be published in relevant international scientific journals. Participant's identity however will remain confidential. By partaking you agree to the publication of such results.
- The participant's task merely involves detection of and response to a target presented on a computer monitor using a handheld button. No invasive techniques will be employed. The exact requirements will be explained thoroughly just prior to task completion.
- Participants are free to withdraw from the study for any reason at any time. Such withdrawal should preferably be accompanied by written communication to such effect.
- If you require any further information as to the nature of the study or participants tasks, please feel free to communicate any questions you may have.

What to do!

- One eye will be covered during the test
- You may be required to wear your spectacles/contacts
- Hold one response button in each hand
- Keep looking straight ahead at the fixation cross throughout the test
- You will be presented with a screen containing 120 items, one of which is different from the rest. Your task is to find the different target. Press the right button if the target appears on the right side of the screen and the left button if on the left
- Respond as quickly as possible once the target appears but accuracy is important. However do not worry if you make an occasional mistake

Many thanks for your co-operation.
Dr Peter Davison and James Loughman; DIT Optometry Department

Appendix 3 – Results Sheet

Preattentive Visual Search Efficiency – Test Results

Study: _____

Patient Name: _____

D.O.B.: _____

Rx Used: _____

Fixation Distance: _____

Filename: _____ Hospital File No.: _____

Date: _____ Time: _____

Test Venue: _____

VISUAL STATUS: _____

_____

_____

_____

(1) RIGHT EYE

Task	Mean	S.D
1	_____	_____
2	_____	_____
3	_____	_____

(2) LEFT EYE

Task	Mean	S.D
1	_____	_____
2	_____	_____
3	_____	_____

Acuity Check: _____

No.of Practice Trials: _____

List of Publications:

1: Loughman, J. & Davison P.A. (2002). Effects of retinal image degradation and perceptual learning on preattentive visual search efficiency for flicker, movement and orientation stimuli. Spatial Vision, 15(2), 248.

2: Davison, P.A. & Loughman, J. (2006). Pre-Attentive Visual Search: Effects of Age and Relevance to Driving. Refereed paper presented at 11th conference of Vision in Vehicles, July 2006.

3: Davison, P.A. & Loughman, J. (2006). Effects of retinal image degradation on pre-attentive visual search (PAVS) efficiency for flicker, movement and orientation stimuli. Ophthalmic and Physiological Optics, 26(5), 456-463.

4: Loughman, J., Davison, P.A. & Flitcroft, D.I. (Under Review). Open angle glaucoma effects on preattentive visual search (PAVS) efficiency for flicker, motion displacement and orientation pop-out tasks. British Journal of Ophthalmology (Submitted August 2006).